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<u>Transtympanic Micropressure Device for Ménière's Disease (e.g., Meniett™ Device) (HCPCS Code E2120)</u>

Ménière's disease (also called idiopathic endolymphatic hydrops) is a disorder of the inner ear. Although the cause is unknown, the disorder probably results from an abnormally large amount of fluid (called endolymph) collecting in the inner ear. The symptoms of Ménière's disease include episodic vertigo (i.e., a sensation of dizziness or spinning), hearing loss, tinnitus (i.e., ringing in the ears), and a sensation of fullness in the affected ear.

The use of a transtympanic micropressure device/low-pressure pulse generator (i.e., Meniett™) (Medtronic Xomed, Jacksonville, FL) has been proposed as an alternative to surgery. The device is prescribed by a physician and delivers low-frequency, low-amplitude pressure pulses within the range of 0–20 centimeter (cm) H_20 to the middle ear via a close-fitting ear cuff and tympanostomy tube. Its mode of action is thought to be transmission of the pulses to the inner ear, promoting the flow of endolymph out of the cochlea, alleviating the hydrops and relieving symptoms. The tympanostomy tube is inserted under local anesthetic in the office setting. The patient then uses the device at home three times per day for approximately three minutes per session. The patient discontinues use when symptoms remit.

U.S. Food and Drug Administration (FDA)

In December 1999, Pascal Medical AB (Sweden) received 510(k) approval from the FDA for the Meniett Low-Pressure Pulse Generator. In 2001, Medtronic Xomed, Inc. (Jacksonville, FL) purchased the device from Pascal Medical. The Meniett Low-Pressure Pulse Generator is classified as a Class II device and is indicated for the symptomatic treatment of Ménière's disease.

Literature Review

Russo et al. (2017) conducted a randomized, double-blind, placebo-controlled, multicenter trial to evaluate the efficacy of portable Meniett low-pressure pulse generator in Meniere disease. The trial included 129 adults presenting Meniere disease not controlled by conventional medical treatment. The protocol included three phases: 1) placement of a transtympanic tube and evaluation of its effect (with patient was excluded if there was resolution of symptoms); 2) randomization: six-week treatment with Meniett or placebo device; 3) removal of the device and six-week follow-up period. The evaluation criteria were the number of vertigo episodes (at least 20 minutes with a 12-hour free interval) and the impact on daily life as assessed by self-questionnaires. Ninety-seven patients passed to the second phase of the study: 49 and 48 patients received the Meniett or placebo device, respectively. In the placebo group, the number of vertigo episodes decreased from 4.3 ± 0.6 (mean ± standard error of the mean) during the first phase to 2.6 ± 0.5 after 6 weeks of treatment, and to 1.8 ± 0.8 after the removal of the device. Similar results were observed in the Meniett device group: 3.2 ± 0.4 episodes during the first phase, 2.5 ± after 6 weeks of Meniett device treatment, and 1.5 ± 0.2 after the third phase. The authors concluded that an improvement of symptoms was evidenced in all patients, with no difference between the Meniett and the placebo device groups.

Van Sonsbeek et al. (2015) reported on a Cochrane review to assess the effects of positive pressure therapy (e.g., the Meniett device) on the symptoms of Ménière's disease or syndrome. The review included five randomized, clinical trials with 265 participants. Regarding primary outcome, control of vertigo, it was not possible to pool data due to heterogeneity in the measurement of the outcome measures. In most studies, no significant difference was found between the positive pressure therapy group and the placebo group in vertigo scores or vertigo days; one study, at low risk of bias, showed a significant difference in one measure of vertigo control in favor of positive pressure therapy. For the secondary outcomes, statistically significant results for loss

or gain of hearing were found. Hearing was 7.38 decibels better in the placebo group compared to the positive pressure therapy group mean difference (MD) (95% CI 2.51 to 12.25; two studies, 123 participants). The severity of tinnitus and perception of aural fullness were either not measured or inadequate data were provided in the included studies. For the secondary outcome functional level, it was not possible to perform a pooled analysis with one study showing less functional impairment in the positive pressure group than the placebo group; another study did not show any significant results. The authors concluded that there is no evidence, from five included studies, to show that positive pressure therapy is effective for the symptoms of Ménière's disease.

The Meniett device has been evaluated in several small clinical trials (Ahsan et al., 2015; Shojaku, et al., 2011; Dornhoffer, et al., 2008, Mattox, et al., 2008; Gates, et al., 2006; Stokroos, et al., 2006; Boudewyns, et al., 2005; Thomsen, et al., 2005; Gates, et al., 2004; Odkvist, et al., 2000) with the number of study participants ranging from 12-62 persons. Ashan et al. (2014) reported results of a systematic literature review (eight studies) and meta-analysis (18 studies). Eight studies reported hearing evaluation and improvement in in pure tone average after Meniett treatment (p=.0085). Data could not be combined for American Academy of Otolaryngology–Head and Neck Surgery functional score due to heterogeneity. Of six studies reporting frequency of vertigo, Meniett treatment significantly reduced frequency of vertigo (p<.0001). Limitations of the study include data derived from uncontrolled and retrospective studies, short follow-up of five months, and small numbers of study participants.

In the randomized controlled trial by Thomsen (2005), patients were evaluated for two months to obtain a baseline, after which tympanostomy tubes were placed, followed by two months without treatment to account for the effect of the tympanostomy tubes. Patients then received either the Meniett device for therapy or a sham device that was identical to the active device but did not give any pressure pulses except a slight pressure increase to 2 cm H20 for five seconds to maintain the leakage test. The authors state that the patients were unable to detect whether they were using the active or placebo device, but the basis for this statement is not discussed. Patients were evaluated at two, four, and eight weeks of use. Outcomes demonstrated significant improvement in functional level and in patient perception of vertigo in those receiving therapy with the Meniett device compared to the control group. There was a nonstatistically significant trend, toward reduced frequency of vertigo in those using the Meniett device. Study limitations include small population, exclusion of a large number of participants, and the inability to determine whether the improvement is related to placement of the tympanostomy tube itself.

Limitations which limit the ability to translate outcomes to routine use of this device include small study populations, lack of blinding and randomization in the majority of studies, and improvement in outcomes in individuals who were treated with the Meniett device as well as other interventions. Further large, randomized controlled trials are necessary to determine the effectiveness of this device to improve health outcomes.

Professional Societies/Organizations

The Equilibrium Committee of the American Academy of Otolaryngology-Head and Neck Surgery published a Policy Statement on Micropressure Therapy for Ménière's disease (AAO-HNS 2008, updated 2016) noted that there is some medical evidence to support the use of micropressure therapy (such as the Meniett device) in certain cases of Meniere's disease. The therapy can be used as a second level therapy when medical treatment has failed and the device represents a largely non-surgical therapy that should be available as one of the many treatments for Meniere's disease.

Use Outside of the US

No relevant information.

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Coding/Billing Information Otolaryngology

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Otolaryngology Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description	Comment
0208T	Pure tone audiometry (threshold), automated; air only	
0209T	Pure tone audiometry (threshold), automated; air and bone	
0210T	Speech audiometry threshold, automated;	
0211T	Speech audiometry threshold, automated; with speech recognition	
0212T	Comprehensive audiometry threshold evaluation and speech recognition (0209T, 0211T combined), automated	

HCPCS Codes	Description
E2120	Pulse generator system for tympanic treatment of inner ear endolymphatic fluid

*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.

Other

Holtranscobalamin Testing (CPT Code 84999)
Vitamin B12, also known as cobalamin is a water soluble vitamin important in normal neurologic functioning and the formation of red blood cells. Measurement of total serum cobalamin may be used to detect a deficiency state (i.e., <200pg/mL). Sensitivity and specificity of this test is poor in part because serum levels do not always correlate with body stores. Only a portion of cobalamin is metabolically active (i.e., transcobalamin). Transcobalamin-cobalamin complex (i.e., holotranscobalamin or holo-TC) testing has been proposed as an alternative measurement of vitamin B12 deficiency. Testing may be by radio- or enzyme immunoassay.

U.S. Food and Drug Administration (FDA)
In January 2004, the HoloTC RIA device (Axis-Shield Biochemicals, ASA, San Diego, CA) was determined by the FDA to be substantially equivalent as an in-vitro diagnostic assay for quantitative measurement of cobalamin (vitamin B12) bound to the carrier protein transcobalamin in human serum or blood.

Literature Review
Randomized controlled trial (RCT) data are scarce in the published peer-reviewed scientific literature regarding the effectiveness of holotranscobalamin testing for the diagnosis of vitamin B12 deficiency or for use in monitoring response to therapy. Hoey et al (2009) reported results of a systematic review which assessed the effectiveness of biomarkers: vitamin B12, methylmalonic acid and total homocysteine in determining vitamin B12 status in eight RCTs. All studies measured serum and plasma total vitamin B12. All biomarkers were found to be effective measures of altered vitamin B-12 intake in populations with low and borderline baseline vitamin B-12 status (p<, 0.00001); however, in the case of total vitamin B-12, substantial heterogeneity that could not be fully explained by subgroup analysis was observed. Insufficient data were available to determine the effectiveness of plasma holotranscobalamin, which was measured in only one RCT.

Use Outside of the US
British Committee for Standards in Hamatology ([BCSH]): The BCSH (Devalia, et al., 2014) published recommendations for the diagnosis and treatment of cobalamin and folate disorders. Regarding holtranscobalamin testing, the Committee notes that serum holotranscobalamin has the potential as a first-line test, but an indeterminate grey area may still exist.

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Multivariate Analysis of Patient Specific Findings with Quantifiable Computer Probability Assessment (CPT Code 99199)
Quantitative pretest probability assessment or attribute matching matches an explicit clinical profile of a patient to a reference database to estimate the numeric value for the pretest probability of disease. It has been proposed that this assessment, which is available at the bedside, may aid the health care professional in making the decision to perform certain diagnostic tests.

According to Kline et al. (2010) attribute matching works by a selection process whereby a computer algorithm compares the results of a selected number of predictor variables obtained from the patient being evaluated to a library of research patients previously evaluated for a specific indication compiled from multiple hospitals. The algorithm returns from the library only the "matched" patients who share the same profile of predictor variables as the patient under consideration and reports the proportion of patients with disease in this matched sample.

The PREtestConsult ACS and PREtestConsult PE modules (BreathQuant Medical Systems, Inc., Charlotte, NC) are a software application that estimates the probability of acute coronary syndrome or pulmonary embolism in adult patients. According to information on the PREtestConsult website, clinical data are entered into the modules by means of a personal data assistant or computer.

Literature Review

Randomized controlled clinical data are limited to evaluate the effectiveness and clinical utility of quantifiable computerized probability assessment. Kline et al. (2009) reported the results of a randomized clinical trial involving 400 adult patients (control group, n=185; intervention group, n=184) who were evaluated for chest pain in a single medical center emergency department. Patients had neither obvious evidence for acute coronary syndrome nor other obvious reasons for admission. After an electrocardiogram was performed clinicians were asked to give their estimate of the percentage probability that the patient would have an acute coronary syndrome-defining event in the subsequent 45 days. Randomization was performed by way of a sealed, sequentially numbered envelope that contained assignment to either the control or intervention group. A member of the research team followed the patient to determine physical disposition status from the emergency department. Patients were contacted by telephone at seven and 45 days after enrollment by a research coordinator who was unaware of group assignment. The mean of the pretest probability estimates from the clinicians was 4 (5%) compared with 4 (6%) for the computerized device estimate. Safety and efficacy endpoints for controls versus intervention patients, respectively, were as follows: (1) delayed or missed diagnosis of acute coronary syndrome: 1 of 185 versus 0 of 184, (2) hospital admission with no significant cardiovascular diagnosis: 11% versus 5%, (3) thoracic imaging imparting greater than 5 mSv radiation with a negative result: 20% versus 9%, (4) median length of stay: 11.4 hours versus 9.2 hours, (5) reported feeling "very satisfied" with clinician explanation of problem on follow-up survey: 38% versus 49%, and (6) readmitted within 7 days: 11% versus 4%. Data suggest that use of a quantitative estimate of the pretest probability of acute coronary syndrome was associated with reduced resource use.

Use Outside of the US

No relevant information.

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<u>Bioimpedance Spectroscopy to Measure Extracellular Fluid Differences Between Limbs (CPT Code 93702)</u>

Bioelectrical impedance analysis is a noninvasive technique measures the body's response to electrical current. Current flows along the path of least resistance through the body and thus follows tissues with the highest water content, allowing measurement of edema (AHRQ, 2010). Bioimpedance spectroscopy has been proposed as a tool to detect early stage lymphedema.

Lymphedema is a pathological condition resulting from an accumulation of protein-rich fluid in the interstitial space because of congenital or acquired damage to the lymphatic system. Acquired or secondary lymphedema may be caused by disease, trauma, or an iatrogenic process such as surgery or radiation (Agency for Healthcare Research and Quality [AHRQ], 2010). Lymphedema is generally staged by observation of the individual's physical condition (i.e., stage 0-3) and is typically diagnosed by clinical history and physical examination. AHRQ notes that it is difficult to detect stage 0 or subclinical lymphedema with current methods. According to a

technology assessment by AHRQ (2010) serial measurement of limb volume and or circumference are de facto gold standards for diagnosing secondary edema; however, no single method of assessment has emerged as the standard comparator for randomized clinical trials (AHRQ, 2010).

U.S. Food and Drug Administration (FDA)

Impedimed L-Dex U400 ExtraCellular Fluid analyzer received FDA 510(k) approval on October 3, 2008 with approval of an expansion of indications on November 4, 2011. According to the approval summary it is "indicated for use on adult human patients, utilizing impedance ratios that are displayed as an L-Dex ratio that supports the measurement of extracellular fluid volume between the limbs and is presented to the clinician as an aid to their clinical assessment of unilateral lymphedema of the arm and leg in woman and the leg in men. The device is only indicated for patients who will have or who have had lymph nodes from the axillary and pelvic regions either removed, damaged or irradiated. The device is not intended to diagnose or predict lymphedema of the extremity."

Literature Review

Erdogan et al. (2015) reported on a study of 37 patients with breast cancer who underwent bioimpedance spectroscopy to assess lymphedema. During a one-year follow-up period where investigators used bioimpedance measures, a stasticially significant relationship was apparent between the incidence of lymphedema and disease characteristics, including the total number of lymph nodes and the region of radiotherapy. The authors concluded that preliminary results indicate that bioimpedance may be a reasonable method regular monitoring to detect lymphedema. The study was limited by the small subject number and the lack of randomization.

Barrio et al. (2015) reported on a prospective study that compared bioimpedance (L-Dex) and volume displacement (VD) measurements in a prospective cohort of 186 breast cancer patients at risk for lymphedema. Patients received baseline VD and L-Dex; with follow-up measurements performed at three-six months intervals for three years. At each visit, patients fitted into one of three categories: normal (normal VD and L-Dex); abnormal L-Dex (L-Dex > 10 or increase in 10 from baseline and normal VD); or lymphedema (relative arm volume difference of >10 % by VD ± abnormal L-Dex). Change in L-Dex was plotted against change in VD; correlation was assessed using the Pearson correlation. At a median follow-up of 18.2 months, 152 patients were normal, 25 had an abnormal L-Dex, and 9 developed lymphedema without a prior L-Dex abnormality. Of the 25 abnormal L-Dex patients, four progressed to lymphedema, for a total of 13 patients with lymphedema. Evaluating all time points, 186 patients had 829 follow-up measurements. Sensitivity and specificity of L-Dex compared with VD were 75 and 93 %, respectively. There was no correlation found between change in VD and change in L-Dex at 3 months (r = 0.31) or 6 months (r = 0.21). The authors concluded that VD and bioimpedance demonstrated poor correlation with inconsistent overlap of measurements considered abnormal. It was found that of patients with an abnormal L-Dex, few progressed to lymphedema; with most patients with lymphedema not having a prior L-Dex abnormality. The authors noted that further studies are needed to understand the clinical significance of bioimpedance.

Hayes published a technology directory report regarding bioelectrical impedance (bioimpedance) analysis for assessment of lymphedema (Hayes, 2015; 2017). The review included 25 comparative studies, including two randomized controlled trials (RCTs) that assessed the use of bioelectrical impedance analysis (BIA) for detection of lymphedema (LE), with sample sizes of 20 to 295 patients known to have LE or at risk for developing LE. The findings of the report noted that there is insufficient evidence to make conclusive statements regarding the impact of BIA on the detection or assessment of LE. Individual studies or single groups of authors with multiple studies have found moderate to high correlation between BIA, circumferential measurements, and perometry; however, accuracy of BIA varied widely depending on reference standards. It was noted that there was only very limited evidence on clinical utility or the impact of BIA on patient management or outcomes.

Controlled clinical trial data are lacking. Published studies are primarily limited to case series and validation studies. A technology review by AHRQ (2010) notes there is consistent evidence to indicate that lymphedema can be reliably measured using circumferential measurements or volume displacement. Additionally the assessment noted that there is insufficient evidence to draw conclusions about the reliability of other measures including tonometry, ultrasound, lymphoscintigraphy, or bioimpedance. The authors reviewed 41 studies related to diagnosis of lymphedema. In one study included in the technology assessment the test of interest involved

differences in the sum of arm circumference between treated and untreated arms in persons with breast cancer. Circumferential differences to diagnose lymphedema were established at ≥5cm and ≥10cm. For differences of ≥5cm versus bioimpedance, sensitivity was 35% and specificity was 89%. For a difference of ≥10cm versus bioimpedance, sensitivity was 5% and specificity was 100%. For self-report compared to bioimpedance, sensitivity was 65%, specificity was 77%. In another included study bioimpedance was used diagnostically in 102 persons with breast cancer. The sensitivity of bioimpedance compared to limb volume was 10% and specificity was 98%. Two included studies involved bioimpedance alone. The first study found that mean and median bioimpedance measures were greater in the arms of women with lymphedema who survived breast cancer. In the other study single-frequency bioimpedance was highly correlated to bioimpendace spectroscopy (r=.99). The authors noted the tests did not drive the choice of treatment or outcome.

Use Outside of the US
No relevant information.

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Near-Infrared Spectroscopy Studies of Lower Extremity Wounds (CPT Code 0493T)

Foot ulceration remains a major health problem for diabetic patients. A standard method for determining the effectiveness of various treatment methods and quantifying wound healing has not been established. Measurements vary from observer to observer and rely on changes in length, width, and depth (Weingarten, et al., 2010). Treatments can include moist wound healing protocols, offloading to reduce the pressure on the wound, active wound healing agents, and/or active therapies such as hyperbaric oxygen and/or negative pressure therapy. Near-infrared spectroscopy has been proposed as a noninvasive method of measuring the optical properties of tissue oxyhemoglobin content of lower extremity wounds beneath the skin surface to guide treatment.

Diffuse photon density wave (DPDW) methodology of near infrared spectroscopy (NIRS) can be used to measure the absolute concentrations of oxyhemoglobin and deoxyhemoglobin in tissue at depths of up to several centimeters. NIRS utilizes a detector and a dispersive element to allow the intensity at different wavelengths to be recorded. More data are needed to determine the threshold value that will distinguish healing from nonhealing wounds (Niedrauer, 2010).

In this procedure the wound is interrogated using a near-infrared spectroscopy device in up to 10 different locations. Data outputs are in the form of concentrations of oxygenated hemoglobin and total hemoglobin in the blood vessels in the wound. Comparing results on a weekly or biweekly basis, the clinician assesses wound healing progression to determine the need for changes in clinical approach.

Literature Review

Randomized controlled clinical trial data are lacking in the published peer-reviewed scientific literature regarding the safety and effectiveness of near-infrared spectroscopy for the measurement of lower extremity wound ealing, including its use for the transcutaneous measurement of oxyhemoglobin. Reisman et al. (2016) reported on a cohort study that examined the use of near-infrared spectroscopy (NIRS) to detect sustained hyperemia following lower extremity trauma. The study examined if NIRS may be a useful monitoring tool for acute compartment syndrome (ACS). Expected normal values for this measurement have yet to be established. The study included 25 cases with acute unilateral lower extremity fractures. NIRS measurements for hemoglobin saturated with oxygen (rSO2) were taken approximately 48 hours after surgical stabilization for each compartment bilaterally, using the contralateral (uninjured) leg as an internal control. Mean rSO2 values taken 48 hours from surgical stabilization from each compartment of the patients' injured legs were significantly higher than the mean values of the contralateral legs (injured = 70, 68, 72, 70; contralateral = 55, 54, 57, 56 for anterior, lateral, deep posterior, and superficial posterior compartments, respectively; $p < 0.0001$ for all compartments). The study was limited by the lack of randomization and small subject number.

Use Outside of the US

No relevant information.

References

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MarginProbe® (CPT Code 19499)

The MarginProbe System technology is based on the principle of radiofrequency (RF) spectroscopy. The technology relies on subjecting tissue to an electric field, and then measuring the tissue response to that field, yielding an electromagnetic signature. According to the manufacturer, the surgeon applies external fields to suspect tissue and captures minute differences in electromagnetic properties. The system compares those responses to an internal database of known signatures in healthy and cancerous tissues (Dune Medical, 2015).

U. S. Food and Drug Administration
In December 27, 2012, MarginProbe® (Dune Medical Devices Inc., Paoli, PA, formerly Farmington, MA) received PMA approval from the Food and Drug Administration (FDA). The Dune MarginProbe®™ System is an adjunctive diagnostic tool for identification of cancerous tissue at the margins (≤ 1mm) of the main ex-vivo lumpectomy specimen following primary excision and is indicated for intraoperative use in conjunction with standard methods (such as intraoperative imaging and palpation) for patients undergoing lumpectomy for previously diagnosed breast cancer.

Literature Review
Hayes published a health technology brief regarding the MarginProbe System (Dune Medical Devices) (Hayes, 2017). The review included seven studies (n=42 to 596) that evaluated the clinical validity, utility, and safety of MarginProbe for intraoperative assessment of surgical margins in patients with breast cancer. Two studies were randomized controlled trials (RCTs), 3 were nonrandomized cohort studies with historical controls, and 2 were prospective cohort studies. One study was determined to be fair quality; four poor quality; and, two of very poor quality. Across studies, the rates of re-excision were statistically significantly lower in patients managed using MarginProbe plus standard of care (SOC) methods when compared with SOC methods alone. While most studies focused on rates of re-excision in patients with positive tumor margins, a critical endpoint—local tumor recurrence—was not evaluated in any study, which precludes any conclusions regarding the impact of the device on clinical oncologic outcomes. Moderate margin-level sensitivity (range, 70% to 75.2%) and low-to-moderate specificity (range, 46.4% to 70%) implies that positive margins could be missed by the device or that healthy tissue could be unnecessarily resected. The review noted study limitations included: use of historical controls; short duration of follow-up; failure to standardize methods used preoperatively to locate nonpalpable lesions; failure to standardize surgical methods and SOC methods to assess specimen margins across study arms; and failure to assess clinically relevant oncologic outcomes such as local recurrence or cancer-free survival rates. Additional studies are needed to determine whether MarginProbe is a useful adjunct to SOC methods for intraoperative margin assessment of breast tumors.

Randomized controlled clinical trial data are limited in the published, per-reviewed scientific literature. Data are primarily in the form of prospective case controlled and retrospective analyses.

Sebastian et al. (2015) reported on a retrospective, observational study that provided compilation of data from routine use of the device, to assess the impact of device utilization on re-excision rates on groups of consecutive patients, before and after the implementation of intraoperative use of the device during lumpectomy procedures. Historical re-excision rates for each surgeon (four surgeons in three centers) were established based on a consecutive set of patients from a time period proximal to initiation of use of the device. In total, 165 cases lumpectomy cases were performed. Positive margins resulted in additional re-excision procedures in 9.7% (16/165) of the cases. The corresponding historical set from 2012 and 2013 consisted of 186 lumpectomy cases, in which additional re-excision procedures were performed in 25.8% (48/186) of the cases. The reduction in the rate of re-excision procedures was significant 62% ($P < 0.0001$). This study is limited by the retrospective nature of the study and small sample size.

Schnabel et al. (2014) published results of a randomized prospective clinical trial evaluating lumpectomy margin assessment with the use of MarginProbe in addition to standard methods in 596 patients with nonpalpable breast malignancies. In the device arm, MarginProbe was used to examine the main lumpectomy specimens and direct additional excision of positive margins. Intraoperative imaging was used in both arms; no intraoperative pathology assessment was permitted. False-negative rates were 24.8 and 66.1 % and false-positive rates were 53.6 and 16.6 % in the device and control arms, respectively. In similar proportions of patients in both arms, the main lumpectomy specimen contained at least one positive margin. In patients with positive margins on initial lumpectomy specimens, an average of two margins was involved, with no difference between the two arms. Surgeons correctly identified all positive margins on the main specimen and removed additional tissue from

those involved margins in 33 of 147 cases (22 %) in the control arm, versus 101 of 163 (62 %) cases in the device arm (p<0.0001). 19.8 % of patients in the device arm underwent second procedures for reexcision of lumpectomy margins compared with 25.8 % of patients in the control arm, representing a 6 % absolute (23 % relative) reduction associated with MarginProbe use. With regard to reexcision procedures that were required because of positive margins originating from the main lumpectomy specimens the control arm rate was 20.8 % compared with 10.0 % in the device arm (p = 0.002).Study limitations included that this study did not test whether the device would allow for less surgery to be performed if the specimens were carefully examined intraoperatively by pathologists, with or without the selective use of frozen section. Although results are promising, additional large randomized trials and consensus support by way of published society/professional organization are necessary before this device can be considered standard of care.

Thill et al. (2014) assessed the benefit of MarginProbe in intraoperative margin assessment during breast conservation surgery (BCS) of ductal carcinoma in situ, the associated reduction of re-excisions and the cosmetic outcome in 42 patients. The study was a multi-center, single arm, post market study enrolling 55 patients and was conducted at three sites in Germany. During the study MarginProbe was used as an adjunctive tool to standard of care. Results were compared to a historical re-excision rate, defined as the number of re-excisions (26/67 patients, 39%) that had been performed on DCIS patients from the general screening. The device use was associated with a reduction in re-excision rates by 56%, from 39% to 17% (p=0.018). In 21% (9/42) of the cases use of the device led to a direct conversion to mastectomy due to extensive disease identified, sparing an additional re-excision BCS. Study limitations include small number of participants and uncontrolled study design.

Allweis et al. (2008) reported results of a randomized clinical trial in 300 patients (device: n=149, control: n=151) assessing a real-time, intraoperative probe for positive margin detection in breast-conserving surgery. In the device group, the probe was applied to the lumpectomy specimen and additional tissue was excised according to device readings. Study arms were compared by reoperation rates and by correct surgical reaction confirmed by histology. In both arms surgeons were allowed to use any standard of care (SOC) intraoperative methods to evaluate margin status such as palpation, specimen imaging, and intraoperative gross and/or microscopic pathology assessment. Pathology data were collected for the primary lumpectomy and all repeat ipsilateral surgical procedures within 6 months. The device was only applied to the main lumpectomy specimen and was not used in reoperations. Reoperation rate between the two groups was not statically significant (p=0.98). The proportion of patients with long-term "excellent" or "good" cosmetic evaluation was similar in both arms (71% and 69% for the two groups, respectively (p=0.71). Data do not suggest improved reoperation rates compared to control.

Use Outside of the US
No relevant information

References

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Optical Coherence Tomography of Breast or Axillary Lymph Node (CPT Codes 0351T, 0352T, 0353T, 0354T)

Optical coherence tomography (OCT) is a high-resolution, near-infrared light imaging modality that has been proposed as a non-surgical method of assessing breast and axillary lymph node margins.

Literature Review

Randomized clinical trial data are lacking in the published, peer-reviewed scientific literature. Butler-Henderson et al. (2014) published a systemic review of 27 studies examining current intraoperative methods for assessing margin status. The final pathology status, statistical measures including accuracy of tumor margin assessment, average time impact on the procedure and second operation rate, were used as criteria for comparison between studies. One third (9/27) of the studies recruited subjects prospectively but did not act on results from intraoperative methods of assessment (IMA), (i.e. prospective observational). About 40% (11/27) of studies also recruited prospectively and acted on IMA results, (i.e. prospective experimental), whereas the remaining (7/27) studies were retrospective chart reviews. Overall, accuracy of IMA was well reported. Accuracy rates for ultrasound, frozen section and optical coherence tomography were 99.6%, 98.02% and 90%, respectively. Imprint cytology had a sensitivity of 80-85% and specificity of 85-100%. Optical coherence tomography reported a sensitivity of 100% and specificity of 82%, but average operation time was unavailable. Only one study examined the use of optical coherence tomography in breast cancer surgery. Additional operation time and second operation rate were not investigated. The authors note that caution is necessary before making any recommendation concerning its use in breast surgery.

Nguyen et al. (2009) reported results of a prospective, observational study. OCT demonstrated a sensitivity of 100% and specificity of 82% for OCT as a real-time method for margin assessment during breast-conserving surgery involving a total of 37 patients. OCT images were acquired from surgical margins of lumpectomy samples. Histologic findings identified nine true positives, nine true negatives, two false positives and no false negatives. The authors concluded that OCT shows potential as a real-time method for intraoperative margin assessment in breast-conserving surgeries. Study limitations include nonrandomized design and small sample size.

References

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2. Butler-Henderson K, Lee AH, Price RI, Waring K. Intraoperative assessment of margins in breast conserving therapy: a systematic review. Breast. 2014 Apr;23(2):112-9.
3. Nguyen FT, Zysk AM, Chaney EJ, et al. Intraoperative evaluation of breast tumor margins with optical coherence tomography. Cancer Res. 2009 Nov 15;69(22):8790-6.

Coding/Billing Information Other

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Considered Experimental/Investigational/Unproven when used to report Margin Probe®:

CPT®* Codes	Description	Comment
19499	Unlisted procedure, breast	Considered Experimental/Investigational/ Unproven when used to report MarginProbe®

Considered Experimental/Investigational/Unproven when used to report multivariate analysis of patient specific findings with quantifiable computer probability assessment:

CPT®* Codes	Description	Comment
99199	Unlisted special service, procedure or report	Considered Experimental/Investigational/ Unproven when used to report multivariate analysis of patient specific findings with quantifiable computer probability assessment

Other Services Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description	Comment
84999	Unlisted chemistry procedure	Considered Experimental/Investigational/ Unproven when used to report Holotranscobalamin, quantitative (Holtranscobalamin Testing)
93702	Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s)	
0351T	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; real-time intraoperative	
0352T	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; interpretation and report, real-time or referred	
0353T	Optical coherence tomography of breast, surgical cavity; real-time intraoperative	
0354T	Optical coherence tomography of breast, surgical cavity; interpretation and report, real-time or referred	
0493T	Near-infrared spectroscopy studies of lower extremity wounds (eg, for oxyhemoglobin measurement)	

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Anoscopy, High Resolution (HRA)

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
46601	Anoscopy; diagnostic, with high-resolution magnification (HRA) (eg, colposcope, operating microscope) and chemical agent enhancement, including collection of specimen(s) by brushing or washing, when performed

46607	Anoscopy; with high-resolution magnification (HRA) (eg, colposcope, operating microscope) and chemical agent enhancement, with biopsy, single or multiple

Whole Body or Selective Head Therapeutic Hypothermia

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
99184	Initiation of selective head or total body hypothermia in the critically ill neonate, includes appropriate patient selection by review of clinical, imaging and laboratory data, confirmation of esophageal temperature probe location, evaluation of amplitude EEG, supervision of controlled hypothermia, and assessment of patient tolerance of cooling

Tumor Treatment Fields (TTF) Therapy (i.e., Optune™)

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type

Considered Experimental/Investigational/Unproven when used to report treatment planning software (i.e., NovoTAL) for use with tumor treatment fields:

CPT®* Codes	Description	Comment
64999	Unlisted procedure, nervous system	Considered Experimental/Investigational/ Unproven when used to report treatment planning software (i.e., NovoTAL) for use with tumor treatment fields

Insertion of Ocular Telescope Prosthesis Including Crystalline Lens

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
0308T	Insertion of ocular telescope prosthesis including removal of crystalline lens or intraocular lens prosthesis

HCPCS Codes	Description
C1840	Lens, intraocular (telescopic)

Margin Probe®

Considered Experimental/Investigational/Unproven when used to report Margin Probe®:

CPT®*	Description	Comment

Codes		
19499	Unlisted procedure, breast	Considered Experimental/Investigational/ Unproven when used to report anoscopy with delivery of thermal energy to the muscle of the anal canal when used to report Margin Probe®

Multivariate Analysis of Patient Specific Findings with Quantifiable Computer Probability Assessment

Considered Experimental/Investigational/Unproven when used to report multivariate analysis of patient specific findings with quantifiable computer probability assessment:

CPT®* Codes	Description	Comment
99199	Unlisted special service, procedure or report	Considered Experimental/Investigational/ Unproven when used to report multivariate analysis of patient specific findings with quantifiable computer probability assessment

Suprachoroidal and Extrascleral Placement of Pharmacologic Agent

Considered Experimental/Investigational/Unproven when used to report suprachoroidal delivery of pharmacologic agent or conjunctival incision with posterior extrascleral placement of pharmacologic agent:

CPT®* Codes	Description	Comment
67299	Unlisted procedure, posterior segment	Considered Experimental/Investigational/ Unproven when used to report suprachoroidal delivery of pharmacologic agent
68399	Unlisted procedure, conjunctiva	Considered Experimental/Investigational/ Unproven when used to report conjunctival incision with posterior extrascleral placement of a pharmacologic agent
0465T	Suprachoroidal injection of a pharmacologic agent (does not include supply of medication	

Additional Services Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description	Comment
32994	Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging	

	guidance when performed, unilateral; cryoablation	
33340	Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation	
34806	Transcatheter placement of wireless physiologic sensor in aneurysmal sac during endovascular repair, including radiological supervision and interpretation, instrument calibration, and collection of pressure data (List separately in addition to code for primary procedure) (Code deleted 12/31/2017)	
34839	Physician planning of a patient-specific fenestrated visceral aortic endograft requiring a minimum of 90 minutes of physician time	
34841	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric, celiac or renal artery)	
34842	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
34843	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
34844	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
34845	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric,	

	celiac or renal artery)	
34846	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
34847	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
34848	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
46999	Unlisted procedure, anus	Considered Experimental/Investigational/ Unproven when used to report transanal radiofrequency therapy for fecal Incontinence (e.g., SECCA procedure)
58674	Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency	
64999	Unlisted procedure, nervous system	Considered Experimental/Investigational/ Unproven when used to report implantation of trial or permanent electrode arrays or pulse generators for peripheral subcutaneous field stimulation
83993	Calprotectin, fecal	
84999	Unlisted chemistry procedure	Considered Experimental/Investigational/ Unproven when used to report Holotranscobalamin, quantitative (Holtranscobalamin Testing)
88749	Unlisted in vivo (eg, transcutaneous) laboratory service	Considered Experimental/Investigational/

		Unproven when used to report skin advanced glycation endproducts measurement by multi-wavelength fluorescent spectroscopy
91112	Gastrointestinal transit and pressure measurement, stomach through colon, wireless capsule, with interpretation and report	
91299	Unlisted diagnostic gastroenterology procedure	Considered Experimental/Investigational/ Unproven when used to report 13C-Spirulina Gastric Emptying Breath Test (GEBT)
92978	Endoluminal imaging of coronary vessel or graft using intravascular (IVUS) or optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; initial vessel (List separately in addition to code for primary procedure)	Considered Experimental/Investigational/ Unproven when used to report CPT code 92978 using endoluminal imaging of coronary vessel or graft using optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; initial vessel
92979	Endoluminal imaging of coronary vessel or graft using intravascular (IVUS) or optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; each additional vessel (List separately in addition to code for primary procedure)	Considered Experimental/Investigational/ Unproven when used to report CPT code 92979 using endoluminal imaging of coronary vessel or graft using optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; each additional vessel
93702	Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s)	
93799	Unlisted cardiovascular service or procedure	Considered Experimental/Investigational/ Unproven when used to report acoustic cardiography
93982	Noninvasive physiologic study of implanted wireless pressure sensor in aneurysmal sac following endovascular repair, complete study including recording, analysis of pressure and waveform tracings, interpretation and report	
94799	Unlisted pulmonary service or procedure	Considered Experimental/Investigational/ Unproven when used to report intermittent

		measurement of wheeze rate for bronchodilator or bronchial challenge diagnostic evaluation
95999	Unlisted neurological or neuromuscular diagnostic procedure	Considered Experimental/Investigational/ Unproven when used to report tremor measurement with accelerometer(s) and/or gyroscope(s)
99199	Unlisted special service, procedure or report	Considered Experimental/Investigational/ Unproven when used to report near-infrared guidance for vascular access requiring real-time digital visualization of subcutaneous vasculature for evaluation of potential access sites and vessel patency
0100T	Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy	
0106T	Quantitative sensory testing (QST), testing and interpretation per extremity; using touch pressure stimuli to assess large diameter sensation	
0107T	Quantitative sensory testing (QST), testing and interpretation per extremity; using vibration stimuli to assess large diameter fiber sensation	
0108T	Quantitative sensory testing (QST), testing and interpretation per extremity; using cooling stimuli to assess small nerve fiber sensation and hyperalgesia	
0109T	Quantitative sensory testing (QST), testing and interpretation per extremity; using heat-pain stimuli to assess small nerve fiber sensation and hyperalgesia	
0110T	Quantitative sensory testing (QST), testing and interpretation per extremity; using other stimuli to assess sensation	
0174T	Computer aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed concurrent with primary interpretation (List separately in addition to code for primary procedure)	
0175T	Computer aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed remote from primary interpretation	
0190T	Placement of intraocular radiation source applicator (List separately in addition to primary procedure)	
0205T	Intravascular catheter-based coronary vessel or graft spectroscopy (eg, infrared) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation, and report, each vessel (List separately in addition to primary procedure)	

0207T	Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral	
0208T	Pure tone audiometry (threshold), automated; air only	
0209T	Pure tone audiometry (threshold), automated; air and bone	
0210T	Speech audiometry threshold, automated	
0211T	Speech audiometry threshold, automated with speech recognition	
0212T	Comprehensive audiometry threshold evaluation and speech recognition (0209T, 0211T combined), automated	
0234T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; renal artery	
0235T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; visceral artery (except renal), each vessel	
0236T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; abdominal aorta	
0237T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; brachiocephalic trunk and branches, each vessel	
0238T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; iliac artery, each vessel	
0254T	Endovascular repair of iliac artery bifurcation (eg, aneurysm, pseudoaneurysm, arteriovenous malformation, trauma, dissection) using bifurcated endograft from the common iliac artery into both the external and internal iliac artery, including all selective and/or nonselective catheterization(s) required for device placement and all associated radiological supervision and interpretation, unilateral	
0255T	Endovascular repair of iliac artery bifurcation (eg, aneurysm, pseudoaneurysm, arteriovenous malformation, trauma) using bifurcated endoprosthesis from the common iliac artery into both the external and internal iliac artery, unilateral; radiological supervision and interpretation (Code deleted 12/31/2017)	
0266T	Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intraoperative interrogation, programming, and repositioning, when performed)	
0267T	Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming and repositioning, when performed)	
0268T	Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)	
0269T	Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)	
0270T	Revision or removal of carotid sinus baroreflex activation	

	device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)	
0271T	Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)	
0272T	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (eg, battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day);	
0273T	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (eg, battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day); with programming	
0293T	Insertion of left atrial hemodynamic monitor; complete system, includes implanted communication module and pressure sensor lead in left atrium including transseptal access, radiological supervision and interpretation, and associated injection procedures, when performed (Code deleted 12/31/2017)	
0294T	Insertion of left atrial hemodynamic monitor; pressure sensor lead at time of insertion of pacing cardioverter-defibrillator pulse generator including radiological supervision and interpretation and associated injection procedures, when performed (List separately in addition to primary procedure) (Code deleted 12/31/2017)	
0337T	Endothelial function assessment, using peripheral vascular response to reactive hyperemia, non-invasive (eg, brachial artery ultrasound, peripheral artery tonometry), unilateral or bilateral	
0338T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral	
0339T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral	
0340T	Ablation, pulmonary tumor(s), including pleura or chest wall when involved by tumor extension, percutaneous, cryoablation, unilateral, includes imaging guidance (Code	

	deleted 12/31/2017)	
0341T	Quantitative pupillometry with interpretation and report, unilateral or bilateral	
0342T	Therapeutic apheresis with selective HDL delipidation and plasma reinfusion	
0351T	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; real-time intraoperative	
0352T	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; interpretation and report, real-time or referred	
0353T	Optical coherence tomography of breast, surgical cavity; real-time intraoperative	
0354T	Optical coherence tomography of breast, surgical cavity; interpretation and report, real-time or referred	
0378T	Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; review and interpretation with report by a physician or other qualified health care professional	
0379T	Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; technical support and patient instructions, surveillance, analysis, and transmission of daily and emergent data reports as prescribed by a physician or other qualified health care professional	
0380T	Computer-aided animation and analysis of time series retinal images for the monitoring of disease progression, unilateral or bilateral, with interpretation and report	
0381T	External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional	
0382T	External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only	
0383T	External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional	
0384T	External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only	
0385T	External heart rate and 3-axis accelerometer data recording more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician	

	or other qualified health care professional	
0386T	External heart rate and 3-axis accelerometer data recording more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only	
0397T	Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (List separately in addition to code for primary procedure)	
0404T	Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency	
0408T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator with transvenous electrodes	
0409T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only	
0410T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only	
0411T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only	
0412T	Removal of permanent cardiac contractility modulation system; pulse generator only	
0413T	Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)	
0414T	Removal and replacement of permanent cardiac contractility modulation system pulse generator only	
0415T	Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead)	
0416T	Relocation of skin pocket for implanted cardiac contractility modulation pulse generator	
0417T	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, implantable cardiac contractility modulation system	
0418T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter; implantable cardiac contractility modulation system	

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HUSKY HEALTH CONNECTICUT

PROVIDER POLICIES & PROCEDURES

ELECTRIC TUMOR TREATMENT FIELD THERAPY (E.G. OPTUNE DEVICE)

The purpose of this document is to assist providers enrolled in the Connecticut Medical Assistance Program (CMAP) with the information needed to support a medical necessity determination for electric tumor treatment field therapy. By clarifying the information needed for prior authorization of services, HUSKY Health hopes to facilitate timely review of requests so that individuals obtain the medically necessary care they need as quickly as possible.

Tumor treatment field (TTF) therapy uses a noninvasive device to create alternating, wave-like electric fields to selectively disrupt mitosis in dividing cancer cells. TTF is approved for use in the treatment of glioblastoma multiforme (GBM), the most prevalent and primary malignant brain tumor in adults. The device is comprised of an electric field generator, a connection cable and box, transducer arrays, and batteries along with a charger, power supply and carrying bag. The transducer arrays are directly applied to the scalp and must be changed at least two times per week. The device is portable for use in normal daily activities and is typically worn for at least 18 hours per day.

CLINICAL GUIDELINE

Coverage guidelines for TTF therapy are made in accordance with the Department of Social Services (DSS) definition of Medical Necessity. The following criteria are guidelines *only.* Coverage determinations are based on an assessment of the individual and their clinical needs. If the guidelines conflict with the definition of Medical Necessity, the definition of Medical Necessity shall prevail. The guidelines are as follows:

Use of a device to generate TTF is generally considered medically necessary for adults (at least 22 years of age) with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma) when used:

1. As monotherapy:
   A. Following histologically or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy; and
   B. When intended as an alternative to standard medical therapy after surgical and radiation options have been exhausted; **OR**
2. As adjunctive therapy with temozolomide for newly-diagnosed histologically confirmed supratentorial glioblastoma following debulking surgery and completion of radiation therapy together with concomitant standard chemotherapy.

Initial Coverage

When all of the above criteria are met, an initial 3 months of TTF therapy will be approved.

Continuing Coverage:

In addition to meeting the above criteria, subsequent approval(s) for continuation of TTF therapy is based on:

1. Evidence of no documented disease progression by MRI or if MRI contraindicated, as evidenced by clinical re-evaluation; and

Please note that authorization is based on medical necessity at the time the authorization is issued and is not a guarantee of payment. Payment is based on the individual having active coverage, benefits and policies in effect at the time of service.

To determine if a service or procedure requires prior authorization, CMAP Providers may refer to the *Benefit and Authorization Grids* summaries on www.ct.gov/husky by clicking on "For Providers" followed by "Benefit Grids". For a definitive list of benefits and service limitations, CMAP Providers may access the CMAP provider fee schedules and regulations at www.ctdssmap.com.

2. Documentation that the individual has been wearing the device for at least 18 hours per day.

The use of a device to generate TTF is generally considered investigational and therefore not medically necessary for the treatment of other malignant tumors (e.g., breast, lung, melanoma, ovarian cancer, pancreatic cancer and solid tumor brain metastases) and for all other indications because the effectiveness has not been established.

The use of combined TTF therapy and chemo-immuno therapy other than temozolomide for the treatment of other malignant tumors is generally considered investigational and therefore not medically necessary because the effectiveness of this approach has not been established.

NOTE: EPSDT Special Provision
Early and Periodic Screening, Diagnosis, and Treatment (EPSDT) is a federal Medicaid requirement that requires the Connecticut Medical Assistance Program (CMAP) to cover services, products, or procedures for Medicaid enrollees under 21 years of age where the service or good is medically necessary health care to correct or ameliorate a defect, physical or mental illness, or a condition identified through a screening examination. The applicable definition of medical necessity is set forth in Conn. Gen. Stat. Section 17b-259b (2011) [ref. CMAP Provider Bulletin PB 2011-36].

PROCEDURE

Prior authorization for TTF therapy is required. Coverage determinations will be based upon a review of requested and/or submitted case-specific information.

The following information is needed to review requests for TTF therapy:

1. Fully completed Outpatient Prior Authorization Request Form or fully completed authorization request via on-line web portal;
2. A prescription from a licensed physician enrolled in the Connecticut Medical Assistance Program (CMAP);
3. Clinical information supporting the medical necessity of the treatment;
4. Pricing information*;
5. Results of follow-up MRI or clinical re-evaluation (when requesting continuing coverage);
6. Documentation that the individual has been wearing the device for at least 18 hours per day (when requesting continuing coverage); and
7. Other information as requested.

* Reimbursed at MSRP – 15%. Payment includes all necessary goods and services related to TTF therapy.

EFFECTIVE DATE

This Policy is effective for prior authorization requests for TTF therapy for individuals covered under the HUSKY Health Program beginning November 1, 2017.

LIMITATIONS

N/A

CODE:

Code	Description
E1399	Durable medical equipment, miscellaneous

DEFINITIONS

1. **HUSKY A**: Connecticut children and their parents or a relative caregiver; and pregnant women may qualify for HUSKY A (also known as Medicaid). Income limits apply.
2. **HUSKY B**: Uninsured children under the age of 19 in higher income households may be eligible for HUSKY B (also known as the Children's Health Insurance Program) depending on their family income level. Family cost-sharing may apply.
3. **HUSKY C**: Connecticut residents who are age 65 or older or residents who are ages 18-64 and who are blind, or have another disability, may qualify for Medicaid coverage under HUSKY C (this includes Medicaid for Employees with Disabilities (MED-Connect), if working). Income and asset limits apply.
4. **HUSKY D**: Connecticut residents who are ages 19-64 without dependent children and who: (1) do not qualify for HUSKY A; (2) do not receive Medicare; and (3) are not pregnant, may qualify for HUSKY D (also known as Medicaid for the Lowest-Income populations).
5. **HUSKY Health Program**: The HUSKY A, HUSKY B, HUSKY C, HUSKY D and HUSKY Limited Benefit programs, collectively.
6. **HUSKY Limited Benefit Program or HUSKY, LBP**: Connecticut's implementation of limited health insurance coverage under Medicaid for individuals with tuberculosis or for family planning purposes and such coverage is substantially less than the full Medicaid coverage.
7. **Medically Necessary or Medical Necessity**: (as defined in Connecticut General Statutes § 17b-259b) Those health services required to prevent, identify, diagnose, treat, rehabilitate or ameliorate an individual's medical condition, including mental illness, or its effects, in order to attain or maintain the individual's achievable health and independent functioning provided such services are: (1) Consistent with generally-accepted standards of medical practice that are defined as standards that are based on (A) credible scientific evidence published in peer-reviewed medical literature that is generally recognized by the relevant medical community, (B)recommendations of a physician-specialty society, (C) the views of physicians practicing in relevant clinical areas, and (D) any other relevant factors; (2) clinically appropriate in terms of type, frequency, timing, site, extent and duration and considered effective for the individual's illness, injury or disease; (3) not primarily for the convenience of the individual, the individual's health care provider or other health care providers; (4) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the individual's illness, injury or disease; and (5) based on an assessment of the individual and his or her medical condition.
8. **Prior Authorization**: A process for approving covered services prior to the delivery of the service or initiation of the plan of care based on a determination by CHNCT as to whether the requested service is medically necessary.

RESOURCES AND REFERENCES:

Government Agency, Medical Society and Other Authoritative Publications:

- Centers for Medicare and Medicaid Services (CMS), Health Care Procedural Coding System Level II Manual: 2017
- CGS Administrators, LLC. Local Coverage Determination (LCD) for Tumor Treatment Field

Please note that authorization is based on medical necessity at the time the authorization is issued and is not a guarantee of payment. Payment is based on the individual having active coverage, benefits and policies in effect at the time of service.

To determine if a service or procedure requires prior authorization, CMAP Providers may refer to the *Benefit and Authorization Grids* summaries on www.ct.gov/husky by clicking on "For Providers" followed by "Benefit Grids". For a definitive list of benefits and service limitations, CMAP Providers may access the CMAP provider fee schedules and regulations at www.ctdssmap.com.

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PUBLICATION HISTORY

Status	Date	Action Taken
Original Publication	September, 2017	Approved at the July 26, 2017 Medical Policy Review Committee meeting. Approved by the Clinical Quality Subcommittee on September 21, 2017. Approved by DSS on September 26, 2017.

MEDICAL POLICY

Excellus

SUBJECT: TUMOR–TREATMENT FIELD THERAPY FOR GLIOBLASTOMA POLICY NUMBER: 6.01.45 CATEGORY: Technology Assessment	EFFECTIVE DATE: 05/28/15 REVISED DATE: 08/18/16 PAGE: 1 OF: 5

- ***If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.***
- ***If a commercial product, including an Essential Plan product, covers a specific service, medical policy criteria apply to the benefit.***
- ***If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.***

POLICY STATEMENT:

I. Based upon our criteria and assessment of peer-reviewed literature, Tumor-Treatment Field (TTF) therapy using the NovoTTF-100A™ System for treatment of recurrent Glioblastoma multiforme (GBM) is considered **medically appropriate** when all of the following criteria have been met:
   A. 1st or 2nd recurrence of GBM; and
   B. The individual has a Karnofsky Performance Status (KPS) of 90 or greater; and
   C. The individual has not received prior treatment with Bevacizumab; and
   D. The device is to be used as monotherapy after failure of standard medical therapy (e.g., chemotherapy, surgery, and radiation therapy).
   E. There is documented evidence the member is compliant with the TTF device during a one month trial period. Compliance is defined as use of the device for 18 hours or more per day during the one month trial period.

II. Based upon our criteria and assessment of peer-reviewed literature, Tumor-Treatment Field (TTF) therapy using the NovoTTF-100A™ System for treatment of newly diagnosed Glioblastoma multiforme (GBM) is considered **medically appropriate** when the following criteria have been met:
   A. The device is to be used as an adjunct with the chemotherapy drug temozolomide (TMZ); and
   B. Following standard treatments that include maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

POLICY GUIDELINES:

I. The NovoTTF-100A™ System will be allowable for up to 6 months if the patient is compliant with the regimen. Continued use after 6 months will require additional documentation to show no progression in the patient's condition.

II. The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).

III. The NovoTTF-100A™ System (Novocure Ltd., Haifa, Israel) was approved by the U.S. Food and Drug Administration (FDA) in April 2011 to deliver TTF therapy and is intended as a treatment for adult patients (22 years of age or older) with confirmed glioblastoma multiforme, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted.

IV. The NovoTTF-100A System (Novocure Ltd, Haifa, Israel) was approved by the U.S. Food and Drug Administration (FDA) in October 2015 to deliver TTF therapy and is intended as a treatment for adult patients (22 years of age or older) with newly-diagnosed glioblastoma multiforme when given along with the chemotherapy drug temozolomide following standard treatments that include surgery, and radiation therapy and chemotherapy used together.

V. The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION:

Glioblastoma multiforme (GBM) is the most common and aggressive primary intracranial tumor with approximately 33% surviving 1 year and less than 5% surviving more than 5 years. Median survival with optimal therapy has been reported to be 10-15 months with most tumors recurring within 7-9 months despite multimodal treatment (e.g. repeat surgery, re-irradiation and chemotherapy). Choice of chemotherapy for treatment in the case of recurrence varies but may include alkylating agents (e.g., lomustine, carmustine, procarbazine), re-treatment with temozolomide, and more recently, bevacizumab either alone or in combination with other agents. Overall survival after recurrence is relatively short even with optimal therapy. New or novel treatments such as TTF therapy are being investigated to improve survival in patients with GBM.

TTF therapy is delivered via the NovoTTF-100A™ System which is a battery-powered, portable device that generates alternating low intensity, intermediate electrical fields (100-300 kHz) by four disposable electrode arrays (replaced 1-2 times per week) that are noninvasively attached to the patient's shaved scalp placed in such a way to encompass the tumor. The alternating low intensity electrical field is thought to disrupt cell division of the cancer cells so that either cell division does not occur or it is ineffective, resulting in death of the cancer cells without harming the normal healthy cells. The device is used by the patient at home on a continuous basis (20-24 h/d) for the duration of treatment, which can last for several months. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.

RATIONALE:

The Food and Drug Administration approval of the NovoTTF-100A system was based on a phase 3, multinational prospective RCT (Stupp et al, 2012). Two hundred thirty-seven patients with relapsed or progressive glioblastoma multiforme (GBM), despite conventional radiotherapy were randomized in a 1:1 ratio to receive TTF therapy (delivered by the NovoTTF-100A System) only (n=120) or the best standard of care chemotherapy (active control) (n=117). The choice of chemotherapy regimens varied, reflecting local practice at each of the 28 participating clinical centers which were across 7 countries. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky Performance Status (KPS) score of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens, and 20% had failed bevacizumab prior to study enrollment. Ninety-seven percent (116) of 120 participants in the TTF group started treatment and 93 participants (78%) completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%) due to noncompliance or the inability to handle the device. For each TTF treatment month, the median compliance was 86% (range, 41%-98%), which equaled a mean use of 20.6 hours per day. In the active control group, 113 (97%) of the 117 assigned participants received chemotherapy and all except 1 individual completed a full treatment course. Twenty-one participants (18%) in the active control group did not return to the treating site and details on disease progression and toxicity were not available. This RCT did not reach its primary end point of improved survival compared with active chemotherapy. With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group compared with 6.0 months in the active control group (hazard ratio, 0.86; 95% confidence interval [CI], 0.66 to 1.12; p=0.27). For both groups, 1-year survival was 20%. The survival rates for 2- and 3-year survival were 8% and 4%, respectively, for the TTF group versus 5% and 1%, respectively, for the active control group. PFS rate at 6 months was 21.4% in the TTF group, compared with 15.1% in the active control group (p=0.13). Objective radiologic responses (partial and complete response) were noted in 14 participants in the TTF group and 7 in the active control group, with a calculated response rate of 14.0% (95% CI, 7.9% to 22.4%) versus 9.6% (95% CI, 3.9% to 18.8%), respectively. Sixteen percent of the TTF participants had grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids. Active control participants experienced grade 2-4 events by organ system related to the pharmacologic activity of chemotherapy agents used; severe (grades 3 and 4) toxicity was observed in 3% of participants. Longitudinal quality of life (QOL) data were available in 63 participants (27%). There were no meaningful differences observed between the groups in the domains of global health and social functioning. However, cognitive, emotional, and role functioning favored TTF therapy, whereas physical functioning favored chemotherapy. Symptom scale analysis was in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF group. In summary, this RCT failed to demonstrate the primary end point of improved survival with TTF therapy in comparison to

chemotherapy. Limitations of the trial included a somewhat heterogeneous patient population, with participants included after progression of 1 or several lines of chemotherapy, as well as the use of different chemotherapy regimens in the control group. Another limitation is the absence of a placebo/supportive care arm. In the setting of advanced disease, the supportive care arm would have been useful to gauge the safety and efficacy of treatment for both groups of patients. Treatments used in the active control arm (best standard of care chemotherapy) in the recurrent disease setting have previously demonstrated limited efficacy, thus limiting the ability to determine the true treatment effect of TTF. Data from a trial of TTF versus placebo, or TTF plus standard chemotherapy versus standard chemotherapy alone would therefore provide a better assessment of treatment efficacy.

A subgroup analysis of patient data of this phase 3 trial (Wong et al, 2014) evaluated the different characteristics of responders and nonresponders in the TTF group compared to the active control group. More patients in the TTF arm were considered responders (14/120 vs 7/117 in the chemotherapy arm.) Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months vs 5.6 months, $p<0.001$), and there was a strong correlation (Pearson's r) between response and OS in the TTF arm ($p<0.001$) but not in chemotherapy arm ($p=0.29$). Compared with the chemotherapy arm, a higher proportion of responders in the TTF arm had a prior low-grade histology (36% vs 0%). These differences in treatment responder groups suggest that TTF therapy may differentially benefit certain types of GBM; however, the small numbers of responders in both groups limits generalizations that can be drawn from this analysis.

Analysis of the NovoTTF-100A™ Patient Registry Dataset (PRiDe) of 457 patients with recurrent GBM who were treated with NovoTTF therapy in the United States between October 2011 and November 2013and comparison to patient data in the Phase 3 trial was performed (Mrugula et al 2014) to provide a larger dataset of patients with recurrent GBM treated with TTF therapy. No new adverse events in the PRiDe group of patients were reported compared to the Phase 3 trial group. However median overall survival was longer in the TTF group in the PriDe group (9.6 months) compared to the TTF group in the Phase 3 trial (6.6 months) or in the active chemotherapy group (6.0 months). Median treatment time was almost double for the TTF PriDe group compared to either the TTF or chemotherapy group in the Phase 3 trial. Favorable prognostic factors in the PriDe group included 75% or more daily compliance of the device, treatment with TTF at first recurrence, no prior treatment with bevacizumab, and Karnofsky Performance Score (KPS) 90 or greater. The authors suggest there are subsets of patients who derive significant benefit from TTF therapy and that TTF therapy using the NovoTTF-100A™ device is safe and efficacious to treat recurrent GBM.

The Food and Drug Administration approval of the NovoTTF-100A system for newly diagnosed glioblastoma multiforme (GBM) was based on the results from a clinical trial involving 695 patients newly diagnosed with GBM that compared those who used the device with temozolomide (TMZ) to those receiving TMZ alone (Stupp, 2015). Patients who used the device along with TMZ lived, on average, about 7 months with no disease progression compared to 4 months for those who had the drug alone. The device plus TMZ group survived for an average of 19.4 months after starting treatment compared to 16.6 months for those who were treated with TMZ alone.

The use of TTF therapy has been described in a number of case series. However, without evidence from additional high quality comparative studies, these studies provide limited additional evidence about whether TTF therapy improves outcomes compared with currently available therapy for GBM.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Central Nervous System (v 1.2015) states that alternating electrical field therapy for glioblastoma may be considered as a treatment option for recurrent disease (Category 2B).

CODES: Number Description

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).

CPT:	There are no specific CPT codes for tumor treatment field therapy.	

HCPCS:	A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
	E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type
ICD9:	191.0-191.9	Malignant neoplasm of brain (code range)
ICD10:	C71.0-C71.9	Malignant neoplasm of brain (code range)

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* key article

KEY WORDS:

Electric field therapy, NovoTTF-100A, glioblastoma.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Tumor Treatment Field Therapy. Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34823&ContrId=389&ver=9&ContrVer=1&CntrctrSelected=389*1&Cntrctr=389&s=41&DocType=Active&bc=AggAAAIAAAAAAA%3d%3d&.

Policy: MP306

Section: Medical Benefit Policy

Subject: Tumor Treatment Fields

I. Policy: Tumor Treatment Fields

II. Purpose/Objective:
To provide a policy of coverage regarding Tumor Treatment Fields

III. Responsibility:
A. Medical Directors
B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

V. Additional Definitions
Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
c. in accordance with current standards of good medical treatment practiced by the general medical community.
d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

Medicaid Business Segment
Medical Necessity shall mean a service or benefit that is compensable under the Medical Assistance Program and if it meets any one of the following standards:

(i) The service or benefit will, or is reasonably expected to, prevent the onset of an illness, condition or disability.
(ii) The service or benefit will, or is reasonably expected to, reduce or ameliorate the physical, mental or development effects of an illness, condition, injury or disability.
(iii) The service or benefit will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for members of the same age.

DESCRIPTION: Tumor Treating Fields, or TTF are low intensity, alternating electric fields within the intermediate frequency range. TTF disrupts cell division through physical interactions with key molecules during mitosis. TTF are generated via pairs of transducer arrays placed directly on the skin's surface in the region surrounding the tumor. The Optune™ delivery system is portable and is designed to allow individuals to continue their daily activities while receiving treatment. This non-invasive treatment is intended as a treatment for adults with histologically-confirmed glioblastoma multiforme (GBM).

INDICATIONS: REQUIRES PRIOR AUTHORIZATION BY A PLAN MEDICAL DIRECTOR OR DESIGNEE

ALL Durable Medical Equipment provided for home use requires advanced determination of coverage. Devices furnished at inpatient or outpatient centers are NOT SEPARATELY REIMBURSABLE.

The Optune™tumor treatment field delivery system may be considered medically necessary when **all of the following** criteria are met:

1. As concomitant therapy with temzolomide in newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy; **and**
   - Member is an adult (defined by the FDA for this device as age 22 years or older); **and**
   - Karnofsky Performance Scale* score of 70 or greater, or Eastern Cooperative Oncology Group (ECOG) performance status** 0-1; **and**
   - Member is capable and agreeable to utilizing the device for a minimum of 18 hours per day

or

2. As a monotherapy for recurrent histologically-or radiologically-confirmed glioblastoma multiforme recurrence in the supratentorial region of the brain after receiving chemotherapy;
   - Member is an adult (defined by the FDA for this device as age 22 years or older); **and**
   - Karnofsky Performance Scale* score of 70 or greater, or Eastern Cooperative Oncology Group (ECOG) performance status** 0-1; **and**
   - Member is capable and agreeable to utilizing the device for a minimum of 18 hours per day

NOTE:

* Karnofsky Performance Status Score:

100	Able to work. Normal; No complaints; No evidence of disease.
90	Able to work. Able to carry on normal activity; Minor symptoms.
80	Able to work. Normal activity with effort; Some symptoms.
70	Independent; not able to work. Cares for self; Unable to carry on normal activity.
60	Disabled; dependent. Requires occasional assistance; cares for most needs.
50	Moderately disabled; dependent. Requires considerable assistance and frequent care.
40	Severely disabled; dependent. Requires special care and assistance.
30	Severely disabled. Hospitalized, death not imminent.
20	Very sick. Active supportive treatment needed.
10	Moribund. Fatal processes are rapidly progressing

**** Eastern Cooperative Oncology Group (ECOG) Performance Status**

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

LIMITATION: Authorization for this device will be for a period of one (1) year.

EXCLUSIONS:
For the Medicare business segment, the use of TTF devices for the treatment of glioblastoma multiforme or any other indication is considered not reasonable and necessary, and therefore **NOT COVERED** per L34823 Tumor Treatment Field Therapy.

For the Medicaid business segment, the use of TTF devices for cancer treatment is considered experimental/investigational and **NOT COVERED** per MCOPS Memo #06/2016-006

The use of TTF devices to treat other malignant tumors (including but not limited to breast, lung, pancreatic, solid tumor brain metastases, ovarian and melanoma) and all other indications is considered Experimental, Investigational or Unproven and therefore, **NOT COVERED.**

Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.

CODING ASSOCIATED WITH: Tumor Treatment Fields
The following codes are included below for informational purposes and may not be all inclusive. Inclusion of a procedure or device code(s) does not constitute or imply coverage nor does it imply or guarantee provider reimbursement. Coverage is determined by the member specific benefit plan document and any applicable laws regarding coverage of specific services. Please note that per Medicare coverage rules, only specific CPT/HCPCS Codes may be covered for the Medicare Business Segment. Please consult the CMS website at www.cms.gov ***or the local Medicare Administrative Carrier (MAC) for more information on Medicare coverage and coding requirements.***

77299 Unlisted procedure, therapeutic radiology clinical treatment planning [when specified as plan for using an electrical stimulation device for TTF]

A4555 Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
E0766 Electrical stimulation device used for cancer treatment, includes all accessories, any type
J8700 Temozolomide, oral, 5 mg
J9328 Injection, temozolomide, 1 mg

LINE OF BUSINESS:
Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy. For PA Medicaid Business segment, this policy applies as written.

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This policy will be revised as necessary and reviewed no less than annually.

Devised: 5/16

Revised: 7/16 (updated line of business specific coverage)

Reviewed: 5/17

Effective Date: October 1, 2016

Subject: Tumor Treating Fields

Overview: Tumor treating fields (TTF) therapy uses alternating electric fields to inhibit cell proliferation and leads to programmed cell death in the treatment of glioblastoma.

Policy and Coverage Criteria:

Harvard Pilgrim considers electric tumor treating fields (TTF) **medically necessary** for the treatment of histologically-confirmed glioblastoma (GBM) in members 18 years of age or older.

Harvard Pilgrim considers TTF **medically necessary** when used with temozolomide (TMZ) for the treatment of adult patients with newly diagnosed, supra-tentorial GBM following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

Harvard Pilgrim considers TTF **medically necessary** for the treatment of recurrent GBM when used as a monotherapy after surgical and radiation options have been exhausted.

Exclusions: Harvard Pilgrim considers TTF **investigational and/ or not medically necessary** for the treatment of any condition not outlined above.

Supporting Information:

1. Technology Assessment

Tumor treating fields uses the Optune system which consists of 4 sets of insulated electrodes and an electric generator. The electrodes are attached to the shaved scalp of the patient who wears the device for at least 18 hours out of the day while low-intensity alternating electric fields are delivered to the tumor area. The alternating electric fields inhibit cell proliferation and lead to programmed cell death. The therapy targets dividing cells to stop tumor growth while sparing normal tissue.

2. Literature Review

Emerging evidence supports the use TTF to treat glioblastoma in adult patients.
Stupp et al (2015) conducted a phase 3 randomized trial to evaluate the efficacy and safety of TTF used in combination with TMZ maintenance treatment after chemoradiation therapy for patients with glioblastoma. The study enrolled 695 patients. The analysis included 210 patients randomized to TTF plus TMZ and 105 randomized to TMZ alone. Analysis was conducted at a median follow-up of 38 months. Median progression-free survival was 7.1 months in the TTF plus TMZ group and 4.0 months in the TMZ alone group. Median overall survival was 20.5 months in the TTF plus TMZ group and 15.6 months in the TMZ alone group. The trial was terminated based on the results of the interim analysis. The authors concluded that, based on the interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTF to maintenance TMZ chemotherapy significantly prolonged progression-free and overall survival.
Mahadevan et al (2015) conducted a retrospective review of 40 patients with malignant gliomas who were treated with TTF or TFF with stereotactic radiosurgery (SRS). All patients had failed TMZ chemo-irradiation. Of the 40 patients, 12 received TTF and SRS. The median overall survival from initiation of TTF was 8 months. Those who were treated with TTF and SRS showed an increase in median overall survival compared with the TTF only group, 4 versus 12 months. The authors concluded there may be a benefit to combining TTF and SRS therapies to treat patients with recurrent glioblastoma.

Vymazal and Wong (2014) analyzed the results from two prior studies with demonstrated radiologic tumor response to single-agent TTF in patients with recurrent glioblastoma. The aim of the analysis was to better characterize tumor response patterns and evaluate associations between response, compliance, and overall survival. The overall response rate across both trials was 15%. Response duration was correlated with overall survival, and median overall survival for responders was 24.8 months. Compliance was linked with both improved response and survival. Seven of 16 responders exhibited tumor growth before shrinkage.

Stupp et al (2012) conducted a phase III trial of chemotherapy-free treatment of TTF (20-24 h/day) versus active chemotherapy in the treatment of patients with recurrent glioblastoma. A total of 120 patients received TTF alone and 117 patients received chemotherapy alone. Median survival was 6.6 months in the TTF group versus 6.0 months in the chemotherapy group, which held no significant difference. There was no difference in 1-year survival rate or progression-free survival rate at 6 months. There were significantly less severe adverse events in the TTF group (6%) versus the chemotherapy group (16%) and the quality of life analyses favored TTF therapy in most domains. The authors concluded that no improvement in overall survival was demonstrated, however efficacy and activity with TTF appears comparable to chemotherapy regimens that are commonly used for glioblastoma. Toxicity and quality of life clearly favored TTF.

Pless and Weinberg (2011) published an expert opinion stating "[t]he proof of concept of TTFields has been well demonstrated in the preclinical setting, and the clinical data seem promising in various tumor types. The side effects of TTFields were minimal and in general consisted of skin reaction to the electrodes. There are a number of ways in which TTFields could be further evaluated, for example, in combination with chemotherapy, as a maintenance treatment, or as a salvage therapy if radiotherapy or surgery is not possible."

Salzberg et al (2008) conducted an open, prospective pilot study to evaluate the safety, tolerability, and efficacy profile of TTF treatment in patients with locally advanced and/or metastatic solid tumors using the NovoTTF100A device. The cohort included 6 patients who were heavily pre-treated with several lines of therapy. Patients received TTF treatment for a minimum of 14 days. No serious adverse events occurred. Outcomes showed a partial response of a skin metastasis from primary breast cancer, 3 cases where tumor growth was arrested during treatment, and 1 case of disease progression. The authors concluded that while the cohort was small, the lack of therapy toxicity and the efficacy observed in data gathered indicates the potential of TTF as a treatment modality for solid tumors.

3. Professional/Governmental Organizations

FDA: Optune is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune with temozolomide (TMZ) is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

For the treatment of recurrent GBM, Optune is indicated following histologically- or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013b.pdf

NCCN: Approval of TTF by the FDA in 2011 for the treatment of recurrent glioblastoma was based on a clinical trial that randomized 237 patients to TTF or chemotherapy. Similar survival was seen in the two arms, and TTF therapy was associated with lower toxicity and improved quality of life. Due to lack of efficacy, not all panelists recommend the treatment.

http://www.nccn.org/professionals/physician_gls/pdf/cns.pdf

Codes:

HCPCS code:

E0766 – Electrical stimulation device used for cancer treatment, includes all accessories, any type

Medically necessary ICD-9 codes:

191.0 – malignant neoplasm of brain – Cerebrum, except lobes and ventricles (i.e. basal ganglia, cerebral cortex, corpus striatum, globus pallidus, hypothalamus, thalamus)
191.1 – malignant neoplasm of the brain – frontal lobe
191.2 – malignant neoplasm of the brain – temporal lobe (i.e. hippocampus, uncus)
191.3 – malignant neoplasm of the brain – parietal lobe
191.4 – malignant neoplasm of the brain – occipital lobe
191.5 – malignant neoplasm of the brain – ventricles (i.e. choroid plexus, floor of ventricles)
191.6 – Cerebellum NOS (i.e. cerebellopontine angle)
191.7 – malignant neoplasm of the brain – brain stem (i.e. cerebral peduncle, medulla oblongata, midbrain, pons)
191.8 – malignant neoplasm of the brain – other parts of the brain (i.e. corpus callosum, tapetum)
191.9 – malignant neoplasm of the brain – brain, unspecified (i.e. cranial fossa NOS)

Medically necessary ICD-10 codes:
C71.0 – malignant neoplasm of cerebrum, except lobes and ventricles (i.e. malignant neoplasm of supratentorial NOS)
C71.1 – malignant neoplasm of frontal lobe
C71.2 – malignant neoplasm of temporal lobe
C71.3 – malignant neoplasm of parietal lobe
C71.4 – malignant neoplasm of occipital lobe
C71.5 – malignant neoplasm of cerebral ventricle
C71.6 – malignant neoplasm of cerebellum
C71.7 – malignant neoplasm of brain stem (i.e. malignant neoplasm of 4th cerebral ventricle, infratentorial malignant neoplasm NOS)
C71.8 – malignant neoplasm of overlapping sites of brain
C71.9 – malignant neoplasm of brain, unspecified

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Electric tumor treatment fields (ETTF) to treat glioblastoma (Optune)™

Print

These services may or may not be covered by your HealthPartners plan. Please see your plan documents for your specific coverage information. If there is a difference between this general information and your plan documents, your plan documents will be used to determine your coverage.

Administrative Process

Prior authorization is not required for electric tumor treatment fields to treat glioblastoma.

Coverage

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Electric tumor treatment fields (ETTF) therapy is generally covered subject to the indications listed below and per your plan documents.

Indications that are covered

Electric tumor treatment fields (ETTF) therapy is covered as follows:

1. For patients with glioblastoma (GBM) that recurs or progresses after initial treatment; or

2. As a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM) in combination with temozolomide; or

3. For the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery, and completion of radiation therapy together with concomitant standard of care chemotherapy; or

4. For the treatment of recurrent GBM following histologically-or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

Indications that are not covered

Electric tumor treatment fields (ETTF) is not covered for any additional indications.

Definitions

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Tumor treating fields (TTFs) therapy uses alternating electric fields to inhibit cell proliferation and lead to programmed cell death. TTF therapy targets dividing cells to stop tumor growth while sparing normal tissue. The Optune™ TTF system is intended to treat patients with glioblastoma by using transducer arrays placed on the patient's scalp according to the tumor's location. Patients use the device on an outpatient basis for at least 18 hours per day for 4 weeks to several months. Intended benefits include stabilizing the disease, having fewer treatment-related adverse events, and improving quality of life.

Codes

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If available, codes for a procedure, device or diagnosis are listed below for informational purposes only, and do not guarantee member coverage or provider reimbursement. The list may not be all inclusive.

Codes	Description
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type
A4555	Electrode/ transducer for use with electrical stimulation device used for cancer treatment, replacement only

Products

This information is for most, but not all, HealthPartners plans. Please read your plan documents to see if your plan has limits or will not cover some items. If there is a difference between this general information and your plan documents, your plan documents will be used to determine your coverage. These coverage criteria may not apply to Medicare Products if Medicare requires different coverage. For more information regarding Medicare coverage criteria or for a copy of a Medicare coverage policy, contact Member Services at **952-883-7979** or **1-800-233-9645**.

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Go to

- Administrative process
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- Definitions
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Policy activity

- 08/21/2013 - Date of origin
- 08/21/2013 - Effective date

Review date

- 07/2015

Revision date

- 04/12/2016

Related content

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Medical Policy:	E-5-005
Topic:	Tumor Treatment Fields (TTF)
Section:	Durable Medical Equipment
Effective Date:	March 20, 2017
Issue Date:	June 4, 2018
Last Reviewed:	May 2018

Electrical fields, known as "tumor treatment fields" (TTF), are created by low-intensity, alternating intermediate frequency (100-200 kilohertz [kHz]) electric currents delivered to the malignant tumor site by insulated electrodes placed on skin surface of the tumor site. As a result of the unique shape and electrical characteristics of dividing tumor cells, TTF exposure may damage the dividing cells through anti-microtubule mechanisms and could stop tumor growth while sparing normal tissue.

This policy is designed to address medical guidelines that are appropriate for the majority of individuals with a particular disease, illness, or condition. Each person's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

Policy Position *Coverage is subject to the specific terms of the member's benefit plan.*

TTF may be considered medically necessary when **ALL** of the following indications are met:

- When it is used as an alternative to standard medical therapy, as a monotherapy; **and**
- For treatment of adult patients (22 years of age or older); **and**
- With histologically-confirmed glioblastoma multiforme; **and**
- Following histologically- or radiologically-confirmed recurrence in the Supratentorial region of the brain; **and**
- After receiving chemotherapy; **and**
- After surgical and radiation options have been exhausted.

OR

TTF may be considered medically necessary when **ALL** of the following indications are met:

- It is used as an adjunct to standard maintenance therapy; **and**
- For treatment for adult patients (22 years of age or older); **and**
- With histologically-confirmed glioblastoma multiforme; **and**
- When it is used with temozolomide; **and**
- With newly diagnosed, supratentorial glioblastoma, **and**
- Following maximal debulking surgery; **and**
- Completion of radiation therapy; **and**

- Together with concomitant standard of care chemotherapy.

TTF is considered experimental/investigational when above criteria are not met or for any other indications, and therefore, not covered because the safety and/or effectiveness of this service cannot be established by the available published peer-reviewed literature.

Procedure Codes
A4555, E0766

Place of Service: Inpatient/Outpatient

Experimental/Investigational (E/I) services are not covered regardless of place of service.

The use of tumor treatment fields is typically an outpatient procedure which is only eligible for coverage as an inpatient procedure in special circumstances, including, but not limited to, the presence of a co-morbid condition that would require monitoring in a more controlled environment such as the inpatient setting.

The policy position applies to all commercial lines of business

Denial Statements

Services that do not meet the criteria of this policy will be considered experimental/investigational (E/I). A network provider can bill the member for the experimental/investigational service. The provider must give advance written notice informing the member that the service has been deemed E/I. The member must be provided with an estimate of the cost and the member must agree in writing to assume financial responsibility in advance of receiving the service. The signed agreement must be maintained in the provider's records.

Links

- Link to Diagnosis Codes
- Link to References

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U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html.

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Horizon BCBSNJ
Uniform Medical Policy Manual

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Policy Number:	042
Effective Date:	07/10/2018
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Subject:
Tumor-Treatment Fields Therapy

Description:

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Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

Populations	Interventions	Comparators	Outcomes
Individuals: · With newly diagnosed glioblastoma multiforme on maintenance therapy after initial treatment	Interventions of interest are: · Tumor treating fields therapy as an adjunct to standard maintenance therapy	Comparators of interest are: · Standard maintenance therapy alone	Relevant outcomes include: · Overall survival · Disease-specific survival · Quality of life · Treatment-related morbidity
Individuals: · With progressive or recurrent glioblastoma multiforme	Interventions of interest are: · Tumor treating fields therapy as an adjunct or alternative to medical therapy	Comparators of interest are: · Standard medical therapy	Relevant outcomes include: · Overall survival · Disease-specific survival · Quality of life · Treatment-related morbidity

Background

Glioblastoma Multiforme

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.[1] GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (eg, bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.[1] The peak incidence for G occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.[2]

Clinical Context and Therapy Purpose

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative o adjunct to medical therapy for progressive or recurrent GBM

Treatment of Newly Diagnosed GBM

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patient may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adju therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O^6-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation (see 'Analysis of MGMT Promoter Methylation in Malignant Gliomas' - Policy #098 in the Pathology Section).

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice (see the Supplemental Information section).[3] For patients with good performance status, the most aggressive treatment (standard radiothera [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to comple RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.

Treatment of Recurrent GBM

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients wit recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (eg, lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that incl hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-f survival rate at 6 months is less than 20%.[4] There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this policy are:

· Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
· Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
· Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

Interventions
TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.[4-6] TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposec inhibit tumor growth by 2 mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells ; apoptosis due to movement of macromolecules and organelles during telophase.[5,6] Preclinical studies have indicated that the electric fields may also make th cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered devi is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's sc is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for tl duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

Comparators
The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.[4]

Outcomes
The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality c life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

Timing
Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

Setting
The setting is outpatient care by an oncologist or neuro-oncologist.

Regulatory Status
In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.[7] The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patient years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®.[8]

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.[9] The device was granted prio review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherap

FDA product code: NZK.

Related Policies

- Analysis of MGMT Promoter Methylation in Malignant Gliomas (Policy #098 in the Pathology Section)
- Radiation Therapy for Primary Craniospinal Tumors and Neurologic Conditions (Policy #100 in the Radiology Section)
- Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas or Metastasis to the Brain (Policy #077 in the Radiology Section)

Policy:
(NOTE: For Medicare Advantage, please refer to the Medicare Coverage Section below for coverage guidance.)

1. Tumor treating fields therapy to treat glioblastoma multiforme is considered ***medically necessary*** as an adjunct to standard maintenance therapy with temozolomide in members with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

· Adult patients ≥18 years of age
· Supratentorial tumor
· Karnofsky Performance Status score ≥70%
· Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).

2. Tumor treating fields therapy is considered ***investigational*** in all other conditions including but not limited to the following situations:

· As an adjunct to standard medical therapy (e.g., bevacizumab, chemotherapy) for members with progressive or recurrent glioblastoma multiforme
· As an alternative to standard medical therapy for members with progressive or recurrent glioblastoma multiforme
· For brain metastases
· For cancer in areas other than the brain.

Medicare Coverage:
There is no National Coverage Determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of Local Medicare Carriers. Nori Healthcare Services, LLC, the Local DME Medicare Carrier for jurisdiction JA, has issued determination L34823 Tumor treatment field therapy. Per LCD L348 Tumor treatment field therapy, (E0766) will be denied as not reasonable and necessary. Per Local Policy Article A52711, HCPCS code A4555 is not valid for billing to Medicare and will be denied an invalid code.

For additional information, refer to Local Coverage Determination (LCD): Tumor Treatment Field Therapy (TTFT) (L34823). Available at: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34823&ContrId=389&ver=14&ContrVer=1&CntrctrSelected=389*1&Cntrctr=389&s=38&DocType=All&bc=AggAAAQAAAAAAA%3d%3d&.

Local Coverage Article: Tumor Treatment Field Therapy (TTFT) - Policy Article (A52711). Available at: https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=52711&ver=10&LCDId=34823&ContrId=389&ContrVer=1&CntrctrSelected=389*1&Cntrctr=389&s=38&DocType=All&bc=AggAAAQAIAAAAA%3d%

***Policy Guidelines**: (Information to guide medical necessity determination based on the criteria contained within the policy statements above.)*

Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth >25% compared with the smallest tum area measured in the patient during the trial or appearance of 1 or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme) The Food and Drug Administration label includes the following notices:

- *Patients should use Optune for at least 18 hours a day to get the best response to treatment*
- *Patients should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment.*

***RATIONALE**: This policy was created in 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update w performed through April 5, 2018.*

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcom are length of life, quality of life, and ability to functionincluding benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whethe magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and t quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized contro trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability t broader clinical populations and settings of clinical practice.

For this review, 3 indications are evaluated: (1) tumor treating fields (TTF) as an adjunct to maintenance chemotherapy in newly diagnosed patients following initial treatment with surgery, radiotherapy and chemotherapy and (2) TTF as an adjunct or (3) alternative to medical therapy (eg, bevacizumab, chemotherap progressive or recurrent glioblastoma multiforme (GBM).

Study Selection
The PICOTS was used to select relevant studies.

- *To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.*
- *To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sough*
- *Within each category of study design, studies with larger sample size studies and longer duration were sought.*

TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

Randomized Controlled Trials
Stupp et al (2017) published results of the EF-14 multicenter, open-label phase 3 RCT that evaluated maintenance therapy with TTF for newly diagnosed GB The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by radiotherapy and chemotherapy (see Table 1). A Karnofsky Performance Status (KPS) score of 70 or higher was an additional inclusion criterion ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patient were randomized in a 2:1 fashion to TTF plus maintenance temozolomide or maintenance temozolomide alone.

All patients were seen monthly for follow-up. Quality of life (QOL) was assessed every 3 months, and magnetic resonance imaging (MRI) was performed ever months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome progression-free survival (PFS), and the secondary outcome was overall survival (OS). The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to TTF following the planned interim analysis.

In 2014, an independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The Food and Drug Administration approved the trial termination, and the trial was closed recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this tim The interim analysis, which the Food and Drug Administration considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015).[11] the time of the interim analysis, data were available for 210 patients randomized to TTF plus temozolomide and 105 patients to temozolomide alone. Follow-u the remainder of the 695 enrolled patients continued after enrollment was closed.

Table 1. Key Randomized Controlled Trial Characteristics for Newly Diagnosed Glioblastoma

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Stupp et al (2017)[10]; EF-14	U.S., E.U., South Korea, Israel	83	2009-2016	· 695 newly diagnosed with GBM and treated by radiochemotherapy · KPS score ≥70	TTF >18 h/d plus maintenance temozolomide (n=466)	Maintenance temozolomide alone (5 d every 28 d for 6 cycles) (n=229)

GBM: glioblastoma multiforme; h/d; hours per day; KPS: Karnofsky Performance Status; TTF: tumor treatment fields.

Results of the final analysis of the EF-14 trial were similar to the interim analysis and are shown in Table 2. Both PFS and OS improved with the addition of T therapy to standard maintenance chemotherapy (ie, temozolomide). PFS increased by 2.7 mo (p<0.001) and OS increased by 4.9 mo (p<0.001) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy (p<0.01).

There was a similar percentage of dropouts at the final analysiswith 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone grou More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In secondary analysis of patients who had not progressed, there was no reduction in health-related quality of life with TTF compared with temozolomide alone aside from "itchy skin".[12] Interpretation of this result is limit by the low percentage of patients who completed the health-related quality of life assessments at follow-up (65.8% of the 655 patients alive at 3 months and 41.7% of the 473 patients alive at 12 months). A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from base analysis.

Table 2. Key Randomized Controlled Trial Results for Newly Diagnosed Glioblastoma

Study	Final N (%)	Median PFS (95% CI), mo	Median OS (95% CI), mo	Systemic Adverse Events, n (%)	Seizures, n (%)	Time to 6-Point Decline in MMSE Score (95% CI), mo
Stupp et al (2017)[10]						
TTF + temozolomide	417 (89)	6.7 (6.1 to 8.1)	20.9 (19.3 to 22.7)	218 (48)	26 (6)	16.7 (14.7 to 19.0)
Temozolomide alone	202 (88)	4.0 (3.8 to 4.4)	16.0 (14.0 to 18.4)	94 (44)	13 (6)	14.2 (12.7 to 17.0)
HR (95% CI)		0.63 (0.52 to 0.76)	0.63 (0.53 to 0.76)			0.79 (0.66 to 0.95)
P value		<0.001	<0.001	0.58		0.01

CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; OS: overall survival; PFS: progression-free survival; TTF: tumor treatment fields.

Tables 3 and 4 display notable gaps identified in this trial, the major limitation is the lack of patient blinding to treatment assignment. However, PFS was asses by investigators who were blinded to treatment and placebo effects on OS were expected to be minimal. Investigators considered it practically unfeasible (due the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

Table 3. Relevance Gaps

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Stupp et al (2017)[10]; EF-14			3. Possible differences in post-progression treatment affecting overall survival		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5 Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4. Study Design and Conduct Gaps

Study; Trial	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Stupp et al (2017)[10]; EF-14		1. No sham control and not blinded to treatment assignment				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence inter and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Th was no sham control, and patients were not blinded to treatment assignment, but PFS was assessed by blinded evaluators, and placebo effects on the object measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin fror the transducers.

TTF Therapy as an Adjunct or Alternative to Medical Therapy for Progressive or Recurrent GBM

Randomized Controlled Trials

The 2011 Food and Drug Administration approval of the NovoTTF-100A System (now called Optune) was based on a phase 3 multinational RCT (EF-11), res of which were published by Stupp et al (2012).[4] This trial compared TTF therapy alone with physician's choice medical therapy in 237 adults who had relapse progressive glioblastoma (see Table 5). Patients had failed conventional treatment with radiotherapy, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Pati characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

Table 5. Summary of Key Randomized Controlled Trial Characteristics for Progressive or Recurrent Glioblastoma

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Stupp et al (2012)[4]; EF-	U.S., E.U., Israel	28	1987-2013	· 237 adults with relapsed or progressive supratentorial	120 patients treated with TTF alone. 93 (78%) completed 1	117 patients treated with physician's choice of medical

11					glioblastoma · KPS score ≥70%	cycle	therapy[a]

EU: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields.

[a] Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (ie, carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincrist

Participants were followed monthly, including laboratory tests. MRI images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. QOL questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was (Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, QOL, and radiologic response end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy (see Table 6). With a median follow-up of 39 months, 9 of patients had died. There was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4 of TTF patients. Severe (grades 3-4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal QOL data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appet loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had a number of limitations (see Tables 7 and 8), that included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control group, 21 (18%) patients did not return t the treatment site, and details on disease progression and toxicity were not available. Longitudinal QOL could be analyzed only for 27% of patients who remai on study therapy for 3 months. The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

Table 6. Summary of Key Randomized Controlled Trial Results for Recurrent or Progressive Glioblastoma

Study; Trial	LTFU, n (%)	Median OS, mo	Progression-Free Survival		Overall Survival (95% CI), %		
			Median, mo	Rate at 6 Months (95% CI), %	1 Year	2 Years	3 Years
Stupp et al (2012)[4]; EF-11							
TTF	23 (22)	6.6	2.2	21.4 (13.5 to 29.3)	20	8 (4 to 13)	4 (1 to 8)
PCC	12 (18)	6.0	2.1	15.1 (7.8 to 22.3)	20	5 (3 to 10)	1 (0 to 3)
HR (95% CI)		0.86 (0.66 to 1.12)	0.81 (0.60 to 1.09)				
P value		0.27	0.16	0.13			

CI: confidence interval; HR: hazard ratio; LTFU: loss to follow-up; PCC: physician's choice chemotherapy; TTF: tumor treating fields.

Table 7. Relevance Gaps

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Stupp et al (2012)[4]; EF-11			2. Physician's choice chemotherapy		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5 Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Gaps

Study; Trial	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Stupp et al (2012)[4]; EF-11		1. Not blinded to treatment assignment		1. 78% of TTF group completed only 1 cycle of therapy, 18% of control group lost to follow-up 1. Longitudinal QOL data were available for 27% of patients		1. Not designed as a noninferiority trial

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
QOL: quality of life.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binery; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence inter and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized Comparative Studies

Kesari et al (2017) conducted a post hoc analysis of the EF-14 trial (see Stupp et al [2017] above) to evaluate the efficacy of TTF in patients who had the first recurrence.[13] Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patie who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM (see Table 9). Patient characteristics and

second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months (see Table 10). In comparison, the group of patients who received TTF therapy in addition to systemic therapy ha median OS of 11.8 months (p=0.043).

A registry study published Mrugala et al (2014) assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting (see Table 9).[14] Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 mo) was reported as superior to that attained in the EF-11 pivotal trial (6.6 mo, p<0.001) (see Table 10). More patients in the PRi registry were treated for first recurrence (33% vs 9%), and more had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported novel or unexpected treatment-related adverse events compared with the EF-11 trial.

Table 9. Characteristics of Key Nonrandomized Trial Results

Study	Study Type	Country	Dates	Participants	TTF	Controls	FU
Kesari et al (2017)[13]	EF-14 post hoc analysis	U.S., E.U., South Korea, Israel	2009-2016	204 patients with first recurrence in the EF-14 trial	144 patients treated with TTF plus second-line chemotherapy	60 patients treated with second-line chemotherapy	12.6 mo
Mrugala et al (2014)[14]	Registry	U.S. (91 centers)	2011-2013	457 patients with recurrent GBM	Patient Registry Dataset (PRiDe)	EF-11	

FU: follow-up; GBM: glioblastoma; TTF: tumor treating fields.

Table 10. Summary of Key Nonrandomized Trial Results

Study	Median OS, mo	Median OS With Bevacizumab, mo	
Kesari et al (2017,[13]; EF-14			
TTF plus chemotherapy	11.8	11.8	
Chemotherapy alone	9.2	9.0	
Hazard ratio (95% CI)	0.70 (0.48 to 1.00)	0.61 (0.37 to 0.99)	
P value	0.049	0.043	
		1-Year OS, %	2-Year OS, %
Mrugala et al (2014)[14]			
PRiDe Registry	9.6	44	30
EF-11	6.6	20	9
Hazard ratio (95% CI)	0.66 (0.05 to 0.86)		
P value	<0.001		

CI: confidence interval; OS: overall survival, TTF: tumor treating fields.

Post hoc analyses of the EF-11 pivotal trial have been reported. Wong et al (2014) published a subgroup analysis to determine characteristics of responders a nonresponders in the active treatment and active treatment control.[15] They found that responders had a lower grade of histology and lower daily dexamethaso use than nonresponders. A second post hoc analysis by Kanner et al (2014) of the EF-11 pivotal trial data was performed to evaluate OS among patients who finished at least 1 complete course of TTF or chemotherapy.[16] The investigators reported that median OS was 7.7 months in the TTF group compared with 5. months in the chemotherapy group (p=0.009). These post hoc analyses are considered to be hypothesis-generating.

Section Summary: TTF Therapy as an Adjunct or Alternative to Chemotherapy for Progressive or Recurrent GBM
The single RCT for TTF as an alternative to chemotherapy reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. The noninferiority of TTF compared with chemotherapy might be considered a sufficient health benefit, if TTF reduced treatment toxicity. However, because the trial was not designed as a noninferiority trial no inferences of noninferiority compared with chemotherapy can be made. Physician's choice therapy during the trial was heterogenous, although analysis indica that survival was not affected by choice of chemotherapy. More patients in the TTF group than in the control group did not complete the treatment course. The number of patients who contributed QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators might have been subje to bias due to the lack of blinding.

A nonrandomized post hoc evaluation of the EF-14 trial suggests that TTF may improve survival when combined with chemotherapy for recurrent GBM. This analysis should be considered hypothesis-generating, and further study in high-quality RCTs is needed.

Summary of Evidence
For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenan therapy, the evidence includes an RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, a treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were n blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limit The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence incluc an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compa with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment wit TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through t provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic

medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies (one of which provided 6 responses and 2 of which provided 1 response each and 1 academic medical center (total of 9 individual responses) while this policy was under review in 2016. There was majority support, but not consensus, fo use of tumor treatment fields therapy as an adjunct to maintenance treatment following initial therapy for glioblastoma multiforme. There was mixed support fo the use of tumor treatment fields as an alternative to chemotherapy in advanced or recurrent glioblastoma multiforme.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2018) include recommendations for the treatment of glioblastoma (see Table 11).[3] For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate O[6] methylguanine-DNA methyltransferase promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric field therapy is a category 1 recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.

Table 11. Guidelines for Adjuvant Treatment of Glioblastoma, by Age and Performance Status

Age, y	KPS Score,%	Treatment Options	Category
≤70	≥60	· Standard RT plus concurrent and adjuvant temozolomide plus TTF · Standard RT plus concurrent and adjuvant temozolomide	1
≤70	<60	· Hypofractionated RT with/without concurrent or adjuvant temozolomide · Temozolomide · Palliative/best supportive care	2A
>70	≥60	· Hypofractionated RT plus concurrent and adjuvant temozolomide · Standard RT plus concurrent and adjuvant temozolomide plus TTF · Temozolomide alone · Hypofractionated brain RT alone	1
>70	<60	· Hypofractionated brain RT alone · Temozolomide alone · Palliative/best supportive care	2A

KPS: Karnofsky Performance Status; RT: radiotherapy; TTF: tumor treating fields.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 12. Of particular note are the phase 3 trials evaluating TTF therapy in non small-cell lung cancer and pancreatic cancer. TTF therapy is an active area of research for mechanisms underlying its effects on cancer cells.

Table 12. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01971281[a]	A Phase II Study of TTFields (150 kHz) Concomitant With Gemcitabine and TTFields Concomitant With Gemcitabine Plus Nab-paclitaxel for Front-line Therapy of Advanced Pancreatic Adenocarcinoma	40	Dec 2017 (ongoing)
NCT01894061[a]	A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma	40	Dec 2018
NCT02663271[a]	A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma	18	Mar 2019
NCT02831959[a]	Pivotal, Open-label, Randomized Study of Radiosurgery With or Without Tumor Treating Fields (TTFields) (150kHz) for 1-10 Brain Metastases From Non-small Cell Lung Cancer (NSCLC) (METIS)	270	Jul 2019
NCT02973789[a]	LUNAR: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields) Concurrent With Standard of Care Therapies for Treatment of Stage 4 Non-small Cell Lung Cancer (NSCLC) Following Platinum Failure	534	Dec 2021
NCT02743078[a]	Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory Recurrent Glioblastoma	85	Aug 2022
NCT03377491[a]	EF-27 Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields, 150kHz) Concomitant With Gemcitabine and Nab-paclitaxel for Front-line Treatment of Locally-advanced Pancreatic Adenocarcinoma (PANOVA-3)	556	Dec 2022

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.]

Horizon BCBSNJ Medical Policy Development Process:

This Horizon BCBSNJ Medical Policy (the "Medical Policy") has been developed by Horizon BCBSNJ's Medical Policy Committee (the "Committee") consistent with generally accepted standards medical practice, and reflects Horizon BCBSNJ's view of the subject health care services, supplies or procedures, and in what circumstances they are deemed to be medically necessary or experimental/ investigational in nature. This Medical Policy also considers whether and to what degree the subject health care services, supplies or procedures are clinically appropriate, in terms type, frequency, extent, site and duration and if they are considered effective for the illnesses, injuries or diseases discussed. Where relevant, this Medical Policy considers whether the subject he care services, supplies or procedures are being requested primarily for the convenience of the covered person or the health care provider. It may also consider whether the services, supplies or procedures are more costly than an alternative service or sequence of services, supplies or procedures that are at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the relevant illness, injury or disease. In reaching its conclusion regarding what it considers to be the generally accepted standards of medical practice, the Committee reviews and considers the following: all credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, physician and health ca provider specialty society recommendations, the views of physicians and health care providers practicing in relevant clinical areas (including, but not limited to, the prevailing opinion within the appropriate specialty) and any other relevant factor as determined by applicable State and Federal laws and regulations.

Index:

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Codes:

(The list of codes is not intended to be all-inclusive and is included below for informational purposes only. Inclusion or exclusion of a procedure, diagnosis, drug or device code(s) does not constit or imply authorization, certification, approval, offer of coverage or guarantee of payment.)

CPT*

HCPCS

A4555
E0766

Electric Tumor Treatment Fields

Humana.

Medical Coverage Policy

Effective Date: 02/22/2018
Revision Date: 02/22/2018
Review Date: 02/22/2018
Policy Number: HCS-0517-006

Change Summary: Updated Description, Medical Terms, References

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Description

Electric tumor treatment fields (ETTFs) are created by low-intensity, alternating intermediate frequency (200 kilohertz [kHz]) electric currents which are delivered to a malignant tumor site via insulated electrodes placed around the region of the body containing the tumor.

ETTF treatment first received US Food and Drug Administration (FDA) approval for monotherapy of adults (22 years age or older) with histologically- or radiologically-confirmed recurrent supratentorial glioblastoma (also known as glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma) following chemotherapy *after* surgery and radiation treatments have been exhausted. The FDA expanded the approval to treat individuals with newly diagnosed GBM when given along with the chemotherapy drug temozolomide following standard treatments that include surgery, chemotherapy and radiation therapy.

For information regarding **temozolomide**, please refer to Temodor (temozolomide) Pharmacy Coverage Policy.

Reportedly, the application of ETTFs to the surface of the scalp disrupts the rapid division of cancer cells within the brain while sparing nonproliferating brain tissue and the normal rate of cell division. An example of a FDA approved ETTF device includes, but may not be limited to, Optune (formerly known as the Novo TTF-100A System).

The Optune system is a portable battery operated device. Treatment parameters are preset by the device manufacturer and no electrical output adjustments are available to individuals; however, they must learn to change and recharge depleted batteries. Individuals carry the device with them to receive continuous treatment, typically recommended for at least 18 hours per day for four weeks. Electrodes must be replaced every few days and the scalp reshaved in order to maintain optimal contact.[9]

ETTFs are being studied as an adjunctive therapy for additional indications which include, but may not be limited to, breast cancer, lung cancer and pancreatic adenocarcinoma. **(Refer to Coverage Limitations section)**

Treatment planning software (eg, NovoTAL) is available and designed to be utilized prior to ETTF treatment. The software purportedly allows the physician to individualize treatment by determining optimal placement of the transducer arrays based on the individual's most recent magnetic resonance imaging (MRI) scan, head size and tumor location.[2] **(Refer to Coverage Limitations section)**

Coverage Determination

All requests for electric tumor treatment fields require review by a medical director.

Humana members may be eligible under the Plan for **ETTFs** for the following indications:

- Absence of any contraindication listed in the Coverage Limitations section; **AND**
- 22 years of age or older; **AND**
- Combined ETTF and temozolomide in individuals with histologically-confirmed newly diagnosed GBM limited to the supratentorial region following maximal

debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy[9]; **OR**

- Monotherapy for individuals diagnosed with histologically- or radiologically - confirmed recurrent GBM limited to the supratentorial region following treatment with chemotherapy *after* surgical and radiation treatments have been exhausted[9]

Coverage Limitations

Humana members may **NOT** be eligible under the Plan for **ETTFs** for any indications other than those listed above including, but may not be limited to:

- If the following contraindications are present:
  - Active implanted medical device (eg, deep brain stimulators, spinal cord stimulators, pacemakers, defibrillators); **OR**
  - Bullet fragments; **OR**
  - Pregnancy; **OR**
  - Shunts; **OR**
  - Skull defects (eg, missing bone with no replacement)[9]; **OR**
- Treatment of other malignant tumors (eg, breast, lung, pancreas)

This is considered experimental/investigational as it is not identified as widely used and generally accepted for any other proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **treatment planning software** for use with ETTFs (eg, NovoTAL). This is considered experimental/ investigational as it is not identified as widely used and generally accepted for the proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Background

Additional information about **glioblastoma** may be found from the following websites:

- American Cancer Society
- National Comprehensive Cancer Network
- National Library of Medicine

Medical Alternatives

Physician consultation is advised to make an informed decision based on an individual's health needs.

Provider Claims Codes

Any CPT, HCPCS or ICD codes listed on this medical coverage policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
64999	Unlisted procedure, nervous system	**Not Covered if used to report any procedure outlined in Coverage Limitations section**
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only	
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type	

Click here to view ICD-10-CM code(s) associated with this medical coverage policy.

Medical Terms

Adenocarcinoma – A form of cancer that involves cells from the lining of the walls of many different organs of the body.

Adjunct – Something joined or added to another thing but not essentially a part of it.

Astrocytoma – A tumor that begins in the brain or spinal cord in small, star-shaped cells called astrocytes.

Debulking – Surgically removing all or most of the substance of a tumor or lesion without removing it entirely.

Electrode – Electrical lead or wire through which current may flow.

Glioblastoma Multiforme – A malignant rapidly growing central nervous system (CNS) tumor.

Histologically-Confirmed – The diagnosis of cancer has been confirmed by examining some of the cancerous tissue under a microscope.

Malignant – Characterized by uncontrolled growth; cancerous, invasive or metastatic.

Monotherapy – Therapy that uses one type of treatment, such as radiation therapy or surgery alone, to treat a certain disease or condition.

Palliative – Reducing the intensity of a disease; ease without curing.

Proliferate – To increase in number or spread rapidly and often excessively.

Radiation Therapy – Cancer treatment in which high levels of energy rays (X-rays) are used to destroy or shrink cancer cells.

Supratentorial – Relating to, occurring in, affecting or being the tissues overlying the tentorium cerebelli.

Temozolomide – A drug that is used for treating cancer, which interferes with the development of cancer cells, slowing their growth and spread in the body.

Tentorium Cerebelli – Arched fold of dura mater that separates the two major parts of the brain, the cerebrum above from the cerebellum below.

Tumor – Abnormal growth of tissue resulting from uncontrolled, progressive multiplication of cells and serving no physiological function; a neoplasm.

WHO Classification of Central Nervous System (CNS) Tumors – Uses molecular parameters in addition to histology to define many tumor entities, which formulates a concept of how CNS tumor diagnoses should be structured in the molecular era. Grading helps to understand the aggressiveness or malignancy of a tumor.

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Independence

Commercial
Medical Policy

Medical Policy Bulletin

Title: Tumor Treating Fields

Policy #: 07.03.26

The below medical or claim payment policy is applicable to the Company's commercial products only. Policies that are applicable to the Company's Medicare Advantage products are accessible via a separate Medicare Advantage policy database.

The Company makes decisions on coverage based on Policy Bulletins, benefit plan documents, and the member's medical history and condition. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Medical Policy Bulletin document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged or new medical literature may have been published. This Medical Policy Bulletin will be reviewed regularly and be updated as scientific and medical literature becomes available. For more information on how Medical Policy Bulletins are developed, go to the About This Site section of this Medical Policy Web site.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's contract.

MEDICALLY NECESSARY

NEWLY DIAGNOSED GLIOBLASTOMA WHEN USED IN ADJUVANT TREATMENT

TTFields are medically necessary and, therefore, covered for adult individuals (22 years of age or older) with newly diagnosed glioblastoma, when the individual meets all of the following criteria:

- Histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma)
- Tumor located in the supra-tentorial region of the brain
- Karnofsky Performance Score above 60
- Completed standard therapeutic options, such as maximum safe debulking surgery, concomitant temozolomide, or radiotherapy
- TTFields is prescribed with adjuvant temozolomide (maintenance)
- Willingness to use the TTFields device daily for at least 18 hours

RECURRENT GLIOBLASTOMA WHEN USED AS A MONOTHERAPY

Alternating electric tumor treating fields (TTFields) are medically necessary and, therefore, covered when used as a monotherapy for adult individuals (22 years of age or older) with recurrent glioblastoma, when the individual meets all of the following criteria:

- Histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma)
- Tumor located in the supra-tentorial region of the brain
- Karnofsky Performance Score above 60
- Completed standard therapeutic options, such as maximum safe debulking surgery or systemic chemotherapy or irradiation
- Willingness to use the TTFields device daily for at least 18 hours

NOT MEDICALLY NECESSARY

TTFields are considered not medically necessary and, therefore, not covered because the available published peer-reviewed literature does not support their use for the treatment of individuals with glioblastoma who have any of the following: an implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted devices in the brain, documented clinically significant arrhythmias, or evidence of increased intracranial pressure.

EXPERIMENTAL/INVESTIGATIONAL

All other uses of TTFields are considered experimental/investigational and, therefore, not covered because their safety and/or effectiveness cannot be established by review of the available published peer-reviewed literature.

REQUIRED DOCUMENTATION

The Company may conduct reviews and audits of services to our members regardless of the participation status of the provider. Medical record documentation must be maintained on file to reflect the medical necessity of the care and services provided. These medical records may include but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

PRESCRIPTION (ORDER) REQUIREMENTS

Before submitting a claim to the Company, the supplier must have on file a timely, appropriate, and complete order for each item billed that is signed and dated by the professional provider who is treating the member. Requesting a provider to sign a retrospective order at the time of an audit or after an audit for submission as an original order, reorder, or updated order will not satisfy the requirement to maintain a

timely professional provider order on file.

PROOF OF DELIVERY
Medical record documentation must include a contemporaneously prepared delivery confirmation or member's receipt of supplies and equipment. The medical record documentation must include a copy of delivery confirmation if delivered by a commercial carrier and a signed copy of delivery confirmation by member/caregiver if delivered by the DME supplier/provider. All documentation is to be prepared contemporaneous with delivery and be available to the Company upon request.

CONSUMABLE SUPPLIES (WHEN APPLICABLE)
The durable medical equipment (DME) supplier must monitor the quantity of accessories and supplies an individual is actually using. Contacting the individual regarding replenishment of supplies should not be done earlier than approximately seven days prior to the delivery/shipping date. Dated documentation of this contact with the individual is required in the individual's medical record. Delivery of the supplies should not be done earlier than approximately five days before the individual would exhaust their on-hand supply.

If required documentation is not available on file to support a claim at the time of an audit or record request, the durable medical equipment (DME) supplier may be required to reimburse the Company for overpayments.

Guidelines

Tumor treating fields (TTFields) for the treatment of newly diagnosed and/or recurrent glioblastoma (GBM) utilizes a portable battery or power supply operated device which produces alternating electrical fields within the human body. TTFields are applied to individuals by electrically insulated surface transducer arrays. TTFields disrupt the rapid cell division exhibited by cancer cells.

TTFields are intended to harness electric fields to arrest the proliferation of tumor cells and to destroy them. The TTFields technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to inhibiting cellular division during mitosis. The fields are said to alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used in the treatment of GMB has been specified to 200kHz.

KARNOFSKY PERFORMANCE STATUS (KPS)

A scale measuring the ability of individuals to perform ordinary tasks. KPS scores range from 0 to 100; a higher score means a person is better able to carry out daily activities.

KPS	Definition
100	Normal; no complaint; no evidence of disease
90	Able to carry on normal activity; minor signs of symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity of do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly

0	Dead

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network® (NCCN®), a not-for-profit alliance of 27 leading cancer centers devoted to patient care, research, and education, is dedicated to improving the quality, effectiveness, and efficiency of cancer care so that patients can live better lives. NCCN® promotes the importance of continuous quality improvement and recognizes the significance of creating clinical practice guidelines appropriate for use by patients, clinicians, and other health care decision-makers. NCCN® provides a clinical practice guideline appropriate for use in the treatment of glioblastoma, both as a new diagnosis and in recurrent disease.

NCCN® provide clinical practice guidelines for central nervous system cancers on a variety of prognostic factors, such as: age, good performance status (KPS≥60) , MGMT promotor status (methylated or unmethylated/indeterminate). When the medically necessary criteria listed in this medical policy are met, the NCCN® clinical practice guidelines endorse the use of TTFields, as follows:

IN THE TREATMENT OF NEWLY DIAGNOSED GLIOBLASTOMA
Maximum resection + carmustine (BCNU) wafer with adjuvant treatments inclusive of standard brain RT (recommended dose is 60 Gy in 2.0 Gy fractions or 59.4 Gy in 1.8 Gy fractions) + concurrent temozolomide and adjuvant temozomide + alternating electric field therapy.

IN THE TREATMENT OF RECURRENT GLIOBLASTOMA
Resection with or without carmustine (BCNU) wafer AND palliative/best supportive care if poor performance, or systemic chemotherapy, or consider reirradiation (category 2B) or alternating electric field therapy for glioblastoma (category 2B).

REGULATORY STATUS

On April 8, 2011, the FDA gave premarket approval for the NovoTTF-100A system (NovoCure Inc. Portsmouth, New Hampshire) for the treatment of adult patients (22 years of age or older) with histologically confirmed glioblastoma multiforme (GBM), following histologically or radiologically confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

On October 5, 2015, the FDA expanded approval for Optune™ (formerly NovoTTF-100A) system for the treatment of adult patients with newly diagnosed, supra-tentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, TTFields are covered as durable medical equipment (DME) under the medical benefits of most of the Company's products when the medical necessity criteria listed in this medical policy are met.

Description

Glioblastoma multiforme (GBM) is the most prevalent and most fatal malignant brain tumor in adults, accounting for nearly 15% of all brain cancers. GBMs account for 46.6% of all malignant tumors with 12,150 new cases predicted annually. Malignant gliomas are histologically heterogeneous and invasive tumors that are derived from neuroglia, or glial cells, whose primary responsibility is to support the central

nervous system's neuron cells. GBMs are classified by the World Health Organization (WHO) as astrocytoma. The WHO provides a grading scale based on the most malignant regions of the tumors. Tumor grades depend upon degree of nuclear atypia, mitotic activity, microvascular proliferation, and necrosis, with increased anaplasia, corresponding to higher tumor grades. The 2007 WHO classification of GBM is a grade IV, indicating the most severe cancer grade, exhibiting rapid tumor growth leading to exceedingly poor prognosis. Eighty percent of individuals diagnosed with GBM will progress to recurrent disease, even after the initial surgical options have been exhausted. Survival expectancy for individuals with newly diagnosed GBM averages between 14.6 to 16.7 months with one-year survival rates of 35%. Following a GBM recurrence, the one-year survival rate is only approximately 20%, and median survival ranges from three to nine months.

Although the prognosis is dismal, the treatment options remain limited. The standard first-line treatment for a GBM is maximum surgical resection of the tumor. The National Comprehensive Cancer Network (NCCN®) has developed clinical practice guidance for the treatment of GBM. At present, the recommended treatment for an individual who is newly diagnosed with a histologically confirmed GBM is: maximum resection surgery, followed by radiotherapy (fractionated focal irradiation in daily fractions of 2 Gray [Gy] given 5 days per week for 6 weeks, for a total of 60 Gy). Gray is a unit of measurement for ionized radiation defined by the absorption of one joule of radiation per one kilogram of matter. In addition to radiotherapy, individuals are treated with concomitant continuous daily temozolomide (75 mg per square meter of body-surface area per day, 7 days per week from the first to the last day of radiotherapy), then subsequent cycles (6) of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28-day cycle). For disease recurrence, standard care includes surgical resection in combination with Gliadel® Wafer, stereotactic radiosurgery, and re-operation for additional tumor resection. Irrespective of the varying treatment protocols between the newly diagnosed and recurrent populations, GBM reoccurrence is still 80% and two-year survival rates remain a mere 27% following initial diagnosis. Acknowledging these dismal treatment outcomes, research has been conducted on new therapeutic agents for the treatment of glioblastoma. Stupp et al developed a new technology called tumor treating fields (TTFields) initially utilized and studied to treat the population with recurrent GBM disease.

TTFields is a technology utilizing electric activity through fields and currents to influence the of polarity of molecules, ions, and the cell membranes found in biological organisms to exert an effect on cellular process and impact cell division. By exposing cancer cells to alternating electric fields of low intensity and intermediate frequency, cellular polarity and ionic energy could be manipulated. This mechanism of action purported by TTFields (alternating electric fields) could selectively arrest cellular division (cytokinesis) in cancer cells by impairing normal mitosis and cytokinesis. TTFields are shown to have no effect on non-dividing cells, but to induce apoptosis in dividing cells. The electric fields interfere with cell division by causing misalignment of highly polarized subunits (microtubule monomers) in the mitotic spindle during the metaphase to anaphase transition and by dielectrophoretic movement of intracellular macromolecules and organelles during telophase. During cytokinesis, TTFields generate non-uniform intracellular fields, pulling organelles towards the neck that separates the newly forming daughter cells. In addition, TTFields interfere with the formation of the mitotic spindle by exerting forces on the charged tubulin subunits. Both processes lead to cell apoptosis and tumor growth inhibition. TTFields exert maximal effects when aligned to a cell's mitotic axis. As a cell's mitotic axis can occur randomly in any direction, additive cytotoxic effects are also observed when TTFields are applied in multiple sequential directions.

Individuals who utilize this technology for the treatment of GBM would need to place four transducer arrays onto their shaved scalp and connected to a portable, battery or power supply operated device (Optune, formerly the NovoTTF-100A system), which is preset to generate 200 kHz electric fields within the brain in two sequentially, perpendicular directions. The intensity of the field is also preset by the manufacturer at >0.7 V/cm. Treatment is intended to be continuous and take place in the home setting to allow the participants to maintain daily activities. Transducer arrays are supplied sterile, and prior to placement of the arrays, the scalp must be shaved carefully to limit the adverse effects (i.e., skin irritation, skin wounding).

Although uninterrupted treatment is recommended, individuals can take treatment breaks of up to an hour, twice per day, for personal needs (i.e., shower).

The electrodes themselves are made from high dielectric constant insulated ceramic discs soldered to a flexible circuit board. The flexible printed circuit incorporates the components required for delivering the current for each ceramic plate and for measuring the temperature. At the set parameters, the electrodes are not reported to cause significant heating due to dielectric losses of the insulation or induced fields in the target tissue.

The Optune system contains a separate software component for the use of clinical treatment planning. The NovoTAL™ system is a workstation based software tool that uses MRI head morphology, tumor size and location measurements, and tissue dielectric properties to optimize the TTFields' distribution and intensity within the tumor by determining the specific region of the brain to treat with the placement of paired arrays. The planning software is intended for use by physicians certified to prescribe electronic TTFields used for the treatment of GBM.

PEER REVIEWED LITERATURE

Kirson et al (2004) evaluated 11 types of cancerous cell lines in more than 500 in vitro culture dishes. The researchers calculated growth rates of the cells and measured cell proliferation. In all cell lines reviewed, each culture dish was exposed to TTFields for a period of 24-hour intervals at 100 kHz (at an intensity of 1.0–1.4 V/cm), which resulted in significant inhibition of cell proliferation. To test the relationship between TTFields' intensity and inhibition of cell proliferation, Kirson et al exposed mouse melanoma and rat glioma cell lines to TTFields of different intensities between 1 and 2.5 V/cm. Furthermore, authors reported that the inhibitory effect of TTFields on cell proliferation increased as intensity increased until complete proliferation arrest was achieved at intensities of 1.4 and 2.25 V/cm in melanoma and glioma cells, respectively. The authors reported on the most relevant findings regarding the prolongation of mitosis, stating in treated cells, mitosis seemed to begin normally but was prolonged for variable periods of time before completing cleavage into two daughter cells. In the 500 cells evaluated, the authors reported TTFields had exemplary effect on the cellular process. In the cells treated with TTFields, mitosis was not complete within the standard 3 hours. TTFields treated cells displayed proliferation arrest, and mitosis lasted on average 124 ± 91 min (mean Standard Deviation [SD], n= 53; 40–541 min), whereas in the controlled cells, the average mitosis duration was 62 ± 8 min from cell rounding to cytokinesis with a mean SD of 12 and a range of 47-78 minutes. Their findings resulted in statistically significant prolongation of mitosis ($P < 0.01$, Mann-Whitney U test).

The authors reported in vivo studies with two animal tumor models. TTFields were generated between implanted (intradermal) wholly insulated wires placed on both sides of the tumor. The researchers placed two sets of paired identical insulated wires on the back of a mouse. The comparative in the mouse study was that only one of the pairs were connected to device, thus only exposing the area under the connected pair to TTFields treatment.

The researchers demonstrated that 100 KHz to 1 MHz alternating direction fields have significant specific effects on dividing cells. They reported that the areas treated with electric field of alternating direction provided evidence that all charges and polar molecules are subjected to forces of alternating direction so that ionic flows and dipole rotation oscillate. The basis of these effects during cytokinesis was shown to be that the unidirectional forces induced by disrupting mitotic spindle formation could result in physical disruption of the cell membrane and ultimately to apoptosis. During mitosis, exposure of cells to those fields results in one-fourth being destroyed as the formation of the cleavage furrow approached complete cell separation and violent membrane protrusions and cells exhibit disruption of microtubule spindle elements. Additionally, the authors reported that the direction of the placed electrical current dictates the magnitude of cellular disruption. Kirson et al concluded that when TTFields are placed parallel to the plane division, cells

exhibited more mitotic failure. Placement of the TTFields arrays is an important instruction when the technology is indicated in the treatment of cancers.

TUMOR TREATING FIELDS FOR THE TREATMENT OF RECURRENT, SUPRA-TENTORIAL GLIOBLAST OMA MULTIFORME

Kirson et al 2007 evaluated a single arm, pilot trial study on the safety and efficacy of TTFields treatment that was performed on 10 participants with recurrent GBM. Efficacy analysis was performed for recurrent GBM persons focusing on time to disease progression (TTP), progression-free survival at 6 months (PFS6), and overall survival (OS) as the primary outcomes for individuals treated with the NovoTTF-100A device. Based on such a small sample size no statistical hypothesis tests were measured. This study measured progression-free survival at 6 months (PFS6), producing a result of 50% (23–77%; 95% confidence interval). Ninety-five percent confidence intervals of survival proportions were calculated using Kaplan–Meier survival curves. The initial pilot study reported two of the ten participants surviving beyond the follow-up period, with the longest participant living for 124.0 weeks, differing from historical averages.

The authored indicated that the pilot study demonstrated TTP and OS values that were more than double the reported historical medians, and reported that TTFields treatment resulted in one complete response which was tumor free, confirmed by MRI ten months after stopping treatment, and one partial response which was still responding seven months after stopping treatment. Both were still progression free two years from treatment initiation. In addition, one participant had minimal response, and four had stable disease for over 4 months before progressing, with the authors suggesting that the device could conceivably halt tumor growth.

The seminal trial, which led to the Food and Drug Administration (FDA) granting approval of TTFields, was a prospective randomized, phase III trial (EF-11) conducted by Stupp et al. (2012). The EF-11 trial assessed TTFields as a monotherapy, without chemotherapy, compared to physician's standard chemotherapy. 237 participants were randomly assigned in a 1:1 ratio to receive either TTFields, (n=120) or an active control entailing the best available chemotherapy prescribed at the local investigator's discretion (n= 117). Participants were all at least 24 years old, with an average age of 54, had Karnofsky performance scores of ≥ 70 with limited other comorbidities. The study design reported that participants would receive baseline examinations and be tested monthly in laboratory. Magnetic resonance imagining (MRI) exams were repeated every second month, and quality of life questionnaires were completed every third month. The researchers allowed any number of prior treatments or recurrences of disease without limits. More than 85% of trial participants had failed two or more prior lines of chemotherapy (i.e., ≥ second recurrence), and nearly 20% had failed (or had a recurrence) while being treated with bevacizumab prior to enrollment. Tumor response and progression were determined by a blinded central radiology review. This study was designed to demonstrate device superiority over the pharmaceutical control.

The trial's primary outcome was overall survival (OS). Secondary endpoints were: progression-free survival (PFS), the percentage of individuals alive and progression-free at 6 months (PFS6), 1-year survival rate, radiological response rate (RR), quality of life, and safety. OS and PFS were computed from randomization until event or censored at last follow-up utilizing Kaplan–Meier survival method, with 2-sided log rank statistics for comparison. The study had an 80 percent power at a significance level of 0.05 to detect a 60 percent increase in median OS (Hazard Ratio [HR] 0.63). All analyses were performed using the intent to treat population of all randomized participants, individuals lost to follow-up were censored at the time of last contact. Treatment compliance limitations were disproportionately observed in the study as only 78% (93/120) completed one full cycle of the TTFields. Nearly a quarter of all participants in the TTFields treatment arm were noncompliant and discontinued, or failed to begin treatment. 113 of 117 participants (97%) in the active control group started chemotherapy, and all but one person completed one full treatment course. The study presented with follow-up limitations. Twenty-one participants randomized to the control group failed to return to the treatment site, limiting information on disease progression and

toxicity. Moreover, quality of life, a secondary outcome of the study, was only available for assessment on 63 or 27% of trial participants.

Compliance was recorded for those individuals in the TTFields arm who began treatment (n=116) by device downloads. The downloads recorded the treatment duration that TTFields therapy was delivered to each participant. The observed median compliance rate was 86 percent (41–98%) during each treatment month, resulting into a mean duration use of 20.6 hours per day. The study acknowledged variance among the level of disease progression (i.e., first recurrence versus multiple) by the participants but failed to produce comparisons amongst the control groups. Missing these comparisons limits the study's ability to determine the overall effectiveness of the TTFields as a monotherapy. Participants received either single agent or a combination of chemotherapeutic regimens. The percentage breakdown for the chemotherapy agents prescribed were as follows: individuals received bevacizumab (31%), or irinotecan (31%), followed by nitrosoureas (25%), carboplatin (13%), temozolomide (11%) or various other agents (5%). However, the study reported that among individuals treated with the active chemotherapy control, survival was not significantly affected by the choice of chemotherapeutic agent ($p = 0.66$).

The statistical analysis of the survival data was tested for proportional hazards and the assumption of proportionality met using the Cox proportional hazards regression model. The Cox model was performed in two steps; first, all protocol pre-specified baseline variables were tested directly for interactions with OS; then a reduced model was performed testing the effect of all variables with significant interaction ($p < 0.05$) with OS together on the treatment effect of TTFields versus active chemotherapy. At a median follow-up of 39 months, 220 trial participants had succumbed to their disease (93%). The primary endpoint failed to demonstrate a significant increase in mean overall survival between the two treatments. Median survival failed to report statistical significance but was marginally higher in the TTFields group compared to active control chemotherapy (6.6 versus 6.0 months, respectively). One-year survival proportion was 20% in both groups and was unable to demonstrate superiority over common chemotherapy treatments. The 2- and 3-year survival rates were reported as 8% (95% CI, 4-13) and 4% (95% CI, 1-8) versus 5% (95% CI, 3-10) and 1% (95% CI, 0-3) for TTFields versus active control, respectively. The reported hazard ratio was 0.86 (95% CI, 0.66-1.12) in favor of TTFields ($p = 0.27$), indicating that TTFields may be at least equivalent and trending toward an improvement as compared to active chemotherapy. The trial failed to report statistically significant device superiority. Participants were not restricted based on prior treatments or recurrences. Many of the participants presented with advanced disease at trial initiation. As many as 40% of participants were included after the third disease occurrence, possibly decreasing the potential benefit from treatment. Trial results showed TTFields as a monotherapy provided similar, not superior, efficacy as best physician's choice chemotherapy in individuals afflicted with recurrent GBM, albeit superior quality of life and less toxicity resulting from treatment with chemotherapy.

Secondary trial outcomes were presented without adjustment. Quality of life measures were assessed using the QLQ-C30 questionnaire with brain-specific module (BN-20), and the measurements were presented as the change from baseline to 3 months for each of the subscale domains and symptoms scale. The researchers reported that both cognitive and emotional functioning were higher in the TTFields group compared to the chemotherapy group, with no difference in global health. The researchers reported that more objective radiological responses (partial and complete responses) were seen in the TTFields group than in the active control chemotherapy group (14 versus 7, respectively). Progression-free survival (PFS) resulted marginally in favor of participants in the TTFields treatment group, with median PFS reported as 2.2 and 2.1 months for TTFields versus the active control group, respectively (HR 0.81, 95% CI 0.60 - 1.09; log rank $p = 0.16$). Authors state progression-free survival at 6 month was 21.4 percent (95% CI 13.5 - 29.3) in the TTFields group and 15.1 percent (95% CI 7.8 - 22.3) in the active control group (chi squared $p = 0.13$). The authors were unable to claim statistical significance for the trial outcomes.

This study was limited by the inability to be blinded, which could introduce bias and compromise the quality of life assessments. Participant knowledge of their active participation limits the pinnacle prognostic factor

by creating bias. The disproportionate dropout rates are concerning. Many individuals stopped treatment prior to completing one month of treatment duration, and these individuals failed to be treated long enough to make substantial contributions to assist with determinations on device effectiveness. High rates of participant cross-over from chemotherapy into device treatment were observed in the study. Due to the nature of this disease and the dismal prognosis for individuals in this patient population, even marginal changes in overall survival and any increase in quality of life are clinically significant findings, as alternative to the current treatment modalities for individuals with recurrent GBM. Based on the slight improvement, trends observed in this trial suggest that treatment with TTFields may be considered an option.

Kanner et al performed a post hoc analysis to study the intent-to-treat (ITT) population in the TTFields treatment versus the best physician's choice chemotherapy. The authors report overall survival was significantly affected by duration that the TTFields device was worn. Not surprising, since this treatment is without a half-life and would require continuous application of the device to demonstrate a reduction in tumor growth. Stratifying population size to augment the desired results, the post hoc analysis measured outcomes within the population who fully completed at least one cycle (four weeks) of TTFields treatment. Based on those modifications, the researchers observed individuals who complied with treatment protocol of ≥ 18 hours daily (n=92) had significantly longer overall survival medians, 7.7 versus 4.5 months than those who used treatment ≤ 18 hours (n=28). Small sample sizes in the study diminish this power of the analysis, and the device may create adherence bias. However, a therapeutic response resulting in an observed mean overall survival increase of three months supports treatment effectiveness when compliance of the treatment protocol is adhered to.

A Patient Registry Dataset (PRiDe) followed 457 persons with recurrent GBM who received TTFields therapy was studied by Mrugala et al in a real-world, phase IV setting. Additional information on the safety and effectiveness of the therapy was assessed in the dataset. The primary outcome of the registry evaluated median overall survival, tolerability of the device, participant compliance and survival, and other prognostic factors. Mrugala reported overall survival (OS) and treatment using Kaplan-Meier methods and Cox proportional hazards model assessed participant characteristics and disease prognostic factors on survival. Evaluation was conducted with log-rank tests to compare OS and daily compliance, prior debulking surgery, Karnofsky Performance Score (KPS), number of recurrence, and prior bevacizumab use.

Overall survival between the PRiDe participants and those treated in the the seminal study with TTFields therapy, and physician's best chemotherapy, increased from 9.6 versus 6.6 versus 6.0 months, respectively. Overall survival rates at one- and two- years increased when compared to treatment arms (TTFields and chemotherapy) from the EF-11 study and PRiDe. As stated above, evidence supported daily compliance as a prognostic factor in TTFields therapy. Participants who achieved the recommended daily compliance of ≥18 hours a day had significantly longer (p=.0001) overall survival — 13.5 months versus 4.0 months when individuals reported less than ≤18 hours. Subgroup analysis of individuals treated at first recurrence (n=152) demonstrated the longest median overall survival, resulting in 20 months. The overall survival reported in the first recurrence population is similar to more recent studies on the newly diagnosed, suggesting that TTFields may be an option as an effective therapy in GBM recurrence, if treatment is initiated at earliest recurrence.

The registry failed to evaluate participant use of combination therapy with TTFields and prescription programs, such as chemotherapy and anti-vascular endothelial growth factor agents. Outside of a clinical trial, the lack of recording information on other medical management regimens for participants resulted in critically missed analyses in demonstrating the effectiveness of TTFields as a therapy, potentially misrepresenting the true effectiveness of the device in the largest studied population. The registry highlights compliance as a key finding, supporting the adaptation of TTFields; however, it failed to record compliance data for more than one-third of all device users. Device safety and tolerability was proven outside of observational settings. Consistent with other trials, the adverse event most commonly observed

was associated with device-related skin irritation.

The registry presented with limitations, including lack of quality of life measures, as these were excluded in the real world follow-up, an important prognostic factor in overall health outcome from the original trial. Heterogeneity limitations exist within the registry as 67% of the total population were male (n=309), possibly significant considering the need to shave a user's scalp for successful placement of the treatment arrays when utilizing this device.

TUMOR TREATING FIELDS FOR THE TREATMENT OF NEWLY DIAGNOSED GLIOBLAST OMA MULTIFORME

Stupp et al. 2015 conducted a multi-center, open-label, randomized phase III trial designed to evaluate the efficacy and safety of TTFields following chemoradiation with temozolomide (TMZ) for treatment of newly diagnosed glioblastoma. The trial enrolled 695 participants with histologically confirmed supra-tentorial glioblastoma, who were progression-free following debulking surgery or biopsy, and who have completed standard concomitant chemoradiotherapy with TMZ. These individuals were randomized (2:1) to receive combination therapy of TTFields plus temozolomide (TMZ) (n=466) or standard maintenance chemotherapy alone using TMZ (n=229). Randomization was stratified by participant characteristics: degree of resection, and O6-methylguanine-DNA methyltransferase (MGMT) methylation status. The primary outcome was progression-free survival (PFS) in the intent-to-treat (ITT) population and was assessed by independent reviewers (80% power; hazard ratio [HR], 0.78; allowing for 10% loss to follow-up; 2-sided α level of 0.05). This study investigated shifted overall survival to a secondary outcome but with equal power (HR, 0.76; 2-sided α = 0.05). To avoid an increase in the risk of a false positive result, overall survival was to only be tested statistically if the PFS was achieved.

In October, 2014, a safety monitoring committee reviewed the findings of an interim analysis reporting on the first 315 participants enrolled in the TTFields plus temozolomide (n=210) and temozolomide (n=105) treatment groups. Pre-specified endpoints were achieved in the intent-to-treat population. After a median follow-up of 38 months (18-60 months), the median PFS in the TTFields plus TMZ arm was 7.1 months from randomization (95% confidence interval [CI], 5.9 - 8.2 months) compared to 4.0 months (95 % CI, 3.3 - 5.2) in the control group ([HR] 0.62; 98.7% CI, 0.43 - 0.89; stratified log-rank, P= 0.001). Overall survival in the per-protocol analysis also showed significant improvement. The combination therapy group (n=196) resulted in median OS of 20.5 months (95% CI, 16.7 - 25.0 months) compared to 15.6 months (95% CI, 13.3 - 19.1 months) in the TMZ alone group (n=84) ([HR], 0.64; 99.4% CI, 0.42 - 0.98; P =0.004). Based on the results of the interim analysis, the trial was terminated, and participants in the control group were allowed to receive TTFields. The termination resulted in eleven individuals in the interim analysis and twenty-six participants overall to cross over and receive TTFields treatment. The study demonstrated the addition of TTFields to temozolomide treatment increased median progression-free survival in the ITT population by 3.1 months.

Per the study design, if tumor progression occurred, second-line chemotherapy was offered by local investigator's practice. Noteworthy, TTFields would continue in the treatment arm, until the second radiological confirmed progression, or clinical deterioration, for a maximum of 24 months. Brain imaging was routinely performed, initially at baseline with contrast-enhanced magnetic resonance imaging (MRI) at two weeks prior to treatment initiation, then in two-month intervals until second radiologically confirmed progression in all study participants. Two-thirds of the TTFields plus TMZ group (n=141) continued treatment with TTFields beyond first tumor progression. The trial design to stop at second tumor progression may have clinical importance when considering the progression of disease and the use of TTFields as a treatment option for individuals transitioning from a new diagnosis into recurrent GBM.

The authors reported median treatment duration of 5.8 months (1 - 58 months) with TTFields. Three-quarters (n=157) of enrollees receiving TTFields adhered to therapy. Protocol adherence was considered

wearing the device ≥ 18 hours per day on average during the first 3 treatment months. Further analyses in the ITT population showed the median overall survival was 19.6 months (95% CI, 16.6 - 24.4 months) in the TTFields plus temozolomide group compared to 16.6 months (95% CI, 13.6 - 19.2 months) in the temozolomide alone group ([HR],0.74 95% CI, 0.56 - 0.98; stratified log-rank P=0.03). The percentage of those affected by GBM alive at 2 years following enrollment was 43% in the TTFields plus temozolomide group and 29% in the TMZ alone group (P=0.006, a 14% increase of participants alive at two years in the treatment arm.

The original publication (interim analysis) of the EF-14 study was limited by the investigators stopping the trial earlier and allowing participant cross over. The interim analysis was completed after the initial 315 enrollees reached 18 month follow-up. The results in the initial per-protocol population only evaluated 196, 84 participants in the combination therapy (TTFields plus TMZ) or the TMZ alone arms, respectively. Additionally, as an open-label trial, no sham or placebo treatment was available for the control group. Investigators deemed the use of sham to be unethical, and unpractical, and therefore the potential power of a placebo cannot be assessed. This may introduce adherence bias. The researchers acknowledge placebo bias would be unlikely to influence overall survival and progression-free survival. Following the original trial, which reported results that failed to provide evidence of statistically significant improvements in median overall survival, the primary study outcome shifted between the two seminal trials. In the original EF-11 trial, the primary endpoint was overall survival, and in this trial researchers adjusted the primary outcome to progression-free survival. The results of this study on newly diagnosed GBM, the addition of TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and improved overall survival.

Stupp et al 2017 reported on the final analysis inclusive of the entire trial population (n=695) from the open-label, randomized phase III trial designed to evaluate the effect of TTFields plus temozolomide (TMZ) versus maintaince TMZ alone on survival for individuals with glioblastoma. Stupp et al previously published the results from an interim analysis on the first 395 participants of the same study. The primary outcomes were consistent to the interim analysis.

The data set was locked on December 28, 2016, and the authors reported median treatment duration of 8.2 months (1 - 82 months) with TTFields. After a medium follow-up of 40 months (34 - 66 months), the median progression-free survival was 6.7 months (95% CI, 6.1 - 8.1 months) for individuals treated with combination therapy versus 4.0 months (95% CI, 3.8 - 4.4 months) for those treated with TMZ alone ([HR] 0.63, 95% CI, 0.52 - 0.76; P <0.001). The secondary outcome reported median overall survival duration of 20.9 months from randomization (95% CI, 19.3 - 22.7 months) in the TTFields plus TMZ group versus 16.0 months (95% CI, 14.0 - 18.4 months) for TMZ only ([HR],0.63; 95% CI, 0.53 - 0.76; P<0.001). Both were found to be statistically and clinically significant. Analyzing the percentage of living participants over selected time periods from randomization resulted in 46% alive at 2 years, 26% alive at 3 years, and 13% alive at 5 years in the combination therapy arm, compared to the TMZ only arm reporting 31% alive at 2 years (p <0.001); 16% at 3 years (P=0.009); and 5% at 5 years (P =0.004). Significant percentage increases across each selected time period favoring adjuvant TTField therapy.

The median time to randomization was equal among the treatment arms with 3.8 month (range 1.7 - 6.2) and 3.7 months (range, 1.4 - 6.3) in the combination therapy, and the TMZ alone treatment groups, respectively. Kaplan-Meier estimates for survival were accessed at 6 months for the rate of progression-free survival between the two treatment groups. The authors reported on progression-free survival at 6 months as 56% (95% CI, 51% - 61%) for the TTFields group and 37% (30% - 44%) with TMZ only (P < 0.001). Cox proportional hazards analyzed both overall survival and progression-free survival across factors: trial arms, age, sex, MGMT status, location, and county of residence. Results using Cox proportional hazards with 95% confidence intervals demonstrated several prognostic factors significantly improved OS; these prognostic factors include: TTFields treatment group (HR, 0.63, 0.53 - 0.76, P<0.001), female sex (HR, 0.76, 0.63 - 0.92, P =.005), MGMT status (HR, 0.50, 0.41 - 0.62; P < 0.001), younger age

(measured continuously, [HR], 0.978 per year, 0.969 - 0.985; P < 0.001), and higher KPS (as a categorical variable in 10 point increments P <0.001).

Interestingly, fifty-five percent of participants had a gross tumor resection (95% of tumor removed) and 13% had only a biopsy performed, results indicating the extent of excision was not statistically significant when investigating overall survival (P= 0.183). The addition of TTFields was not associated with an increase in systemic adverse events (AE) (48% versus 44%; P=0.58). Higher rates of AE found in the TTFields treated group were attributed to longer duration of TMZ treatment in the experimental group as a result of delayed disease progression. Investigators report inclusive criteria for TTFields treatment utilizing Karnofsky Performance Score (KPS). KPS is a scale measuring the ability of individuals to perform ordinary tasks. KPS scores range from 0 to 100; a higher score means a person is better able to carry out daily activities. The author reported time to sustain 10 point reduction in KPS significantly longer for the combination group versus the group treated with only TMZ (5.5 months; 95% CI, 5.0 - 6.3 months versus 3.9 months; 95% CI, 3.1 - 5.2 months, respectively; [HR], 0.80; 95% CI, 0.67 - 0.95; P =0.009).

Potentially important for future studies, a small majority of the experimental population (51%; n=237) continued TTFields treatment beyond first treatment progression. The investigators may want to evaluate, in the newly diagnosed population who elect to continue TTFields as a combination therapy beyond first progression, whether significant improvements are observed in progression-free survival and OS compared to the outcomes of the historical recurrent population. The recurrent population only has the option to utilize TTFields as a monotherapy. The largest study to date utilizing the TTFields technology presented with similar limitations as observed in the interim analysis (no sham, burden of use when utilizing the device). Another limitation in the final analysis was that quality of life data points were not recorded. Also, participant heterogeneity limitations exist since nearly 70% of the study participants were male and 89% were white.

The final analysis for the treatment of glioblastoma utilizing the TTFields technology demonstrated that the combination therapy of TTFields and temozolomide chemotherapy following standard concomitant TMZ and radiotherapy has shown to significantly improve progression-free survival and overall survival in the newly diagnosed population.

NovoCure Inc. of Portsmouth, New Hampshire (subsidiary of NovoCure Ltd., Haifa, Israel) was granted approval for the NovoTTF-100A system. The NovoTTF-100A Treatment Kit received US Food and Drug Administration (FDA) Premarket Approval on April 8, 2011 (P100034). The current supplement Optune™ System, which received FDA Premarket Approval on October 5, 2015 (P1000034/S013) was submitted to expand the indications for use: Optune™ System with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supra-tentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

In summary, TTFields has been demonstrated to be a safe and effective alternative treatment, and should be considered for individuals with either recurrent or newly diagnosed Glioblastoma. In 2015, The National Comprehensive Cancer Network® (NCCN®) clinical practice guidelines appropriateness in the treatment of central nervous system cancer for use of TTFields has shifted to consider category 3 in the recurrent population as a category 2B. A 2B category allows providers to consider the use of TTFields in treatment of recurrent disease. The NCCN® 2016 guidelines classifies alternating electronic fields therapy as a 2A grade for newly diagnosed glioblastoma individuals. NCCN® guidelines demonstrate TTFields used in concomitant treatment with adjuvant temozolomide following radiotherapy and concomitant temozolomide for the newly diagnosed. Indicating that use of TTFields could be used an initial treatment therapy, when prescribed with adjuvant temozolomide.

TUMOR TREATING FIELDS IN OTHER INDICATIONS

Researchers have initiated evaluations utilizing NovoCure's TTFields technology in the treatment of other

solid tumor indications. The various populations actively being investigated include cancers such as: non-small cell lung (NSCLC), brain metastases (1-5; 1-10) from NSCLC, pancreatic, ovarian, mesothelioma, and high grade glioma and ependymoma in children. Each of these separate indications has been either recently completed or is actively being studied in phase II trials to determine safety and efficacy with this new modality. The trials range in size, n= 5 in the child study to 82 participants in the mesothelioma trial. Variance exists between the primary outcomes researched in each of the new indications. In the ovarian and pancreatic cancers, the primarily investigated outcome was device related adverse effects and feasibility based on compliance as a result of the individual's early discontinuation of treatment. The tumor location could be a factor in compliance. Toxicity was the principal measurement in the non-small cell lung cancer study, whereas overall survival was the primary outcome in the mesothelioma trial. All studies listed time to progression, or progression-free survival as a secondary endpoint.

Non-small cell lung cancer is currently under investigation, with participants actively enrolled into a prospective, randomized controlled phase III trial aimed to test the efficacy and safety of TTFields in combination with PD-1 inhibitors or docetaxel as a second-line treatment. The researchers will assess the overall survival of participants with the TTFields and docetaxel or PD-1 inhibitors versus docetaxel or PD-1 alone in a superiority study design. Interestingly, if the primary outcome fails, the researchers will evaluate overall survival of those treated with TTFields and docetaxel versus PD-1 inhibitors alone in a separate, more challenging non-inferiority study. This study has a completion date of December 2020.

Evaluation of a trial on the feasibility of Optune for children with recurrent or progressive supra-tentorial high-grade glioma and ependymoma cancers was initiated in early 2017. This trial aims to demonstrate use of the Optune device as a feasible treatment option in the pediatric population and report treatment-related toxicities assessed by Common Terminology Criteria for Adverse Events v4.0. A total of 25 children are expected to participate in this trial. This study was the first trial, inclusive of the pivotal trials, that utilizes the TTFields technology that was not funded or sponsored by the device manufacture, NovoCure, Ltd. The pediatric study is sponsored by Pediatric Brain Tumor Consortium, with support from the National Cancer Institute (NCI).

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility , benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company .

The Coding T able lists any CPT , ICD-9, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear .

> CPT Procedure Code Number(s)

N/A

Professional and outpatient claims with a date of service on or before September 30, 2015, must be billed using ICD-9 codes. Professional and outpatient claims with a date of service on or after October 1, 2015, must be billed using ICD-10 codes.

Facility/Institutional inpatient claims with a date of discharge on or before September 30, 2015, must be billed with ICD-9 codes. Facility/Institutional inpatient claims with a date of discharge on or after October 1, 2015, must be billed with ICD-10 codes.

➤ ICD - 10 Procedure Code Number(s)

N/A

Professional and outpatient claims with a date of service on or before September 30, 2015, must be billed using ICD-9 codes. Professional and outpatient claims with a date of service on or after October 1, 2015, must be billed using ICD-10 codes.

Facility/Institutional inpatient claims with a date of discharge on or before September 30, 2015, must be billed with ICD-9 codes. Facility/Institutional inpatient claims with a date of discharge on or after October 1, 2015, must be billed with ICD-10 codes.

➤ ICD -10 Diagnosis Code Number(s)

C71.0 Malignant neoplasm of cerebrum, except lobes and ventricles

C71.1 Malignant neoplasm of frontal lobe

C71.2 Malignant neoplasm of temporal lobe

C71.3 Malignant neoplasm of parietal lobe

C71.4 Malignant neoplasm of occipital lobe

C71.5 Malignant neoplasm of cerebral ventricle

C71.8 Malignant neoplasm of overlapping sites of brain

➤ HCPCS Level II Code Number(s)

A4555 Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only

E0766 Electrical stimulation device used for cancer treatment, includes all accessories, any type

➤ Revenue Code Number(s)

N/A

Policy History

07.03.26:

03/23/2018	This new policy has been issued to communicate the Company's coverage position.

Version Effective Date: 03/23/2018
Version Issued Date: 03/23/2018
Version Reissued Date: N/A

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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Tumor Treating Fields Therapy

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Criteria
For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Tumor Treatment Fields Therapy (L34823)
Medical Director Article	Tumor Treatment Field Therapy (TTFT) – Response to Comments

For Non-Medicare Members
I. Tumor-treating fields (TTF) to treat primary (not recurrent) supratentorial glioblastoma multiforme (GBM) may be considered medically necessary when **ALL of the following** are met:
   A. Patient is 18 years of age or older; and
   B. Karnofsky Performance Status* is 70% or higher; and
   C. Documentation of histologically-confirmed primary glioblastoma multiforme; and
   D. Patient has completed standard concomitant chemoradiation with temozolomide(TMZ); and
   E. Disease did not progress through chemo radiation (possible "pseudo progression" does not exclude patients from receiving TTF) and
   F. TTF will be administered concurrently with TMZ, unless TMZ has been ineffective, not tolerated, or is contraindicated and
   G. TTF must be started no later than 60 days from the end of chemo radiation

II. Continued treatment of TTF can be covered until the second radiological progression (meaning 2 consecutive images showing tumor progression) or clinical deterioration

All authorizations are for 90 days. Re-authorizations require updated clinical notes and imaging.

*Karnofsky Performance Status Scale

Condition	Value (%)	level of Functional Capacity
Able to carry on normal activity and to work; no special care needed	100%	No complaints; no evidence of disease
	90%	Able to carry on normal activity; minor signs or symptoms of disease
	80%	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70%	Cares for self; unable to carry on normal activity or to do active work
	60%	Requires occasional assistance but is able to care for most personal needs
	50%	Requires considerable assistance and

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		frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; diseases may be progressing rapidly	40%	Disabled; requires special care and assistance
	30%	Severely disabled; hospital admission indicated although death not imminent
	20%	Very sick; hospital admission necessary; active supportive treatment necessary
	10%	Moribund; fatal processes progressing rapidly
	0%	Dead

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, KPWA will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations..

Background

Glioblastoma (GBM), an incurable disease, has the highest incidence rate (3.19/100,000 population) amongst the central nervous system (CNS) tumors with an average survival of 15 months (Thakkar et al., 2014). Numerous genetic and environmental risk factors have been investigated but none is associated with a large population of GBM (Wrensch, Minn, Chew, Bondy, & Berger, 2002). The median age of diagnosis is 64 years and GBM is frequently found in the supratentorial region (Adams et al., 2013). GBM is an aggressive malignancy with poor prognosis and low survival. The first year relative survival rate is 35% and this estimate decreases over time (Ostrom et al., 2013) making the long term survival very harsh. Standard treatment consists of resection with combination of radiation and chemotherapy. These therapies, whether combined or utilized alone, do not significantly decrease mortality and do not lack adverse effects. Because GBM infiltrates the brain, it is prone to recurrence. Management of recurrence became challenging and therefore indispensable for better clinical outcomes. Different therapeutic options have been investigated but tumor treating fields (TTFields), a novel treatment, seems comparable to standard chemotherapy including Temozolomide and is less toxic (Roger Stupp et al., 2012).

TTFields, developed by NovoCure Ltd, is a medical device for the treatment of recurrent GBM. It is a portable, non-invasive, battery-operated and wearable device that disrupts the division of cancer cells and proliferation in the supratentorial region by delivering low-intensity and intermediate frequency (200 kHz) alternating electric fields via transducer arrays applied to the scalp by means of hypoallergenic ceramic disks, which are placed on the scalp using Hydrogel (Axelgaard Manufacturing Co, Ltd, Fallbrook, CA) as a conductor; It is believed that TTFields inhibits cytokinesis and microtubule assemble, and therefore inhibiting growth and causing death of cancer cells (Butowski, Wong, Mehta, & Wilson, 2013). The NovoTTF-100A received premarket approval from the Food and Drug Administration (FDA) on April 10, 2011 for treatment in adult patients with confirmed GBM, following confirmed recurrence in an upper region of the brain after receiving chemotherapy. The device is intended to be used independently and as an alternative to standard medical therapy after surgical and radiation options have been exhausted (FDA 2011).

The review of the safety and effectiveness of TTFields Therapy for the treatment of recurrent GBM in adults has been reviewed previously. However, it is being reviewed based on a request from the Clinical Review Unit with a focus on the combination of TTFields plus Temozolomide as maintenance therapy on newly diagnosed GBM. It is also being reviewed for coverage decision support.

Medical Technology Assessment Committee (MTAC)

Tumor Treatment Fields Therapy

08/19/2013: MTAC REVIEW

Evidence Conclusion: The randomized phase III trial sought to compare the overall survival of subjects treated with the NovoTTF-100A alone to subjects treated with the best standard of care (BSC) chemotherapy available for recurrent GBM (Stupp, Wong et al. 2012). In the clinical study, 237 subjects with previously diagnosed GBM who experienced recurrence of their tumor or their condition worsened despite conventional therapy (surgery and chemo-radiotherapy followed by chemotherapy) were randomly assigned to receive either NovoTTF-100A stand-alone treatment or the BSC chemotherapy (as determined by the local physician). The primary endpoint for the

study was overall survival, as assessed by the log-rank test in the intent-to-treat population. In addition, the study examined the safety and tolerability of NovoTTF-100A treatment based on the incidence and severity of adverse events and toxicities. Secondary endpoints measured in the study included the progression free survival rate at 6 months, time to progression, one year survival rate, quality of life and radiological response rate. The ITT population includes all subjects who were randomized to the trial. At a median follow up of 39 months 93% of patients had died. The analysis was performed by the treatment group to which the subject was randomized. The study results showed that overall survival with the NovoTTF-100A System was no superior to that seen with active best standard of care chemotherapy. There was a slightly higher incidence of neurological adverse events in the NovoTFF-100A treated group (43.1%) compared to the best standard of care control group (36.3%). Mild to moderate skin irritation beneath the device electrodes was seen in 16% of NovoTFF-100A-treated subjects. NovoTFF-100A treated subjects experienced a lower frequency of the classic adverse events as seen with chemotherapy (such as gastrointestinal, hematological and infectious adverse events) with the best standard of care. Quality of life surveys indicated an improved quality of life in the NovoTFF-100A recurrent GBM subjects compared to the best standard of care recurrent GBM subjects. The trial was generally well designed and conducted with recruitment from 28 different clinics, randomization and minimal loss to follow up. Limitations identified by the authors include the somewhat heterogenous patient population with patients included after progression of one or several lines of prior chemotherapy. The authors also observed that the study could have benefited from a placebo or treatment-free control arm. Some limitations that are not highlighted by the authors include the decreasing number of subjects remaining after 12 months which may limit the ability to reliably estimate the long term survival outcomes. Furthermore, it is important to note that the primary investigator, as well as a number of other authors had financial and professional ties with the manufacturer of the device Novocure Ltd., Rye Beach, New Hampshire. Although the study failed to show that the NovoTTF-100A treatment is superior to chemotherapy with respect to overall survival the NovoTTF-100A treatment exhibits minimal toxicity, has clinically comparable primary and secondary effectiveness and better quality of life compared to the chemotherapies used in the control arm of the study.
Articles: A literature search was conducted revealing a small pilot trial and one larger pivotal study. The pilot study was an open-label prospective single arm study to assess the safety and effectiveness of TTFields for the treatment of GBM. The pivotal study was prospective, open label, best standard of care randomized control trial to compare the overall survival of subjects treated with NovoTTF-100A alone to subjects treated with the best standard of care chemotherapy available for recurrent GBM. In addition, the search revealed a case study illustrating one patient's success with TTFields therapy and one expert opinion article discussing the concept, evidence and future of TTFields. The clinical study that formed the FDA's basis for determining that the NovoTTF-100A System is safe and effective for its intended use was selected for review: Stupp R, Wong ET, Kanner AA, Steinberg D, Engelhard H, et al. NovoTFF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomized phase III trial of a novel treatment modality. *European Journal of Cancer.* 2012;48, 2192-2202. See Evidence Table.

The use of TT Fields Therapy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Tumor Treating Fields plus Temozolomide as maintenance therapy for Glioblastoma Multiforme (GBM)
03/21/2016: MTAC REVIEW
Evidence Conclusion: The previous review on TTFields, completed in 2013, aimed to determine the safety and efficacy of TTFields therapy compared to standard medical therapy, for the treatment of recurrent GBM for adult patients. The study evaluating NovoTTF-100A versus Physician Choice Chemotherapy in recurrent glioblastoma (Roger Stupp et al., 2012) was reviewed and no improvement in overall survival was identified. The author of the review concluded that there was insufficient evidence to determine the safety and effectiveness of TTFields Therapy. Stupp, R., S. Taillibert, et al. (2015). "Maintenance Therapy With Tumor-treating Fields plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial." See Evidence Table 1. This randomized phase 3 trial, open label, parallel design, multicenter, (R. Stupp et al., 2015) intended to assess the efficacy and safety of TTFields in combination with temozolomide for treatment of patients with GBM after initial treatment with chemoradiation. After patients were diagnosed, they were initially treated with chemoradiation comprised of Temozolomide and concomitant radiation. Brain MRI was required 2 weeks prior to starting the maintenance treatment (to exclude progression cases). After completion of the initial treatment, patients were randomized at a ratio of 2 to 1 to receive TTFields + Temozolomide (n=466) or Temozolomide alone (n=229).TTFields was initiated within 4-7 weeks from the last dose of concomitant chemoradiotherapy. While Temozolomide was given on a basis of 150-200 mg/m2/d for 5 days every 28 days for 6-12 cycles, TTFields was delivered continuously (>18 hours/day) via 4 transducer arrays placed on the shaved scalp and connected to a portable medical device. The primary outcome was progression-free survival (PFS) in the intent-to-treat population (significance level of 0.01) and the secondary outcome was the overall survival (OS) in the per-protocol population (significance level of 0.006). Safety and tolerability were also evaluated. A total of 695 patients were recruited but

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the trial was terminated after the interim analysis showed a benefit in Progression Free Survival. This interim analysis was conducted after the first 315 randomized patients reached a minimum of 18-month follow-up. Thus, data from 315 patients with 210 patients in the intervention group and 105 patients in the control group were analyzed. Baseline characteristics were nearly similar across the groups with median age of 57 years. The findings were based on the interim analysis. Patients who were treated with TTFields plus Temozolomide had longer PFS [7.1 months (CI, 5.9 – 8.2)] than those who were treated with Temozolomide alone [4 months (95%CI, 3.3 – 5.2)]. Likewise, patients who were treated with TTFields plus Temozolomide had longer OS [20.5 months (16.7 - 25)] than those who were treated with Temozolomide alone [15.6 months (CI, 13.3 – 19.1)]. In addition, no major increases in toxic effects were associated with the intervention. The most common adverse events were thrombocytopenia, mild to moderate skin irritation, and general disorders. In conclusion, the combination of TTFields plus Temozolomide prolonged PFS as well as OS compared to Temozolomide alone for the maintenance treatment of patients with GBM. However, this is an interim analysis with less than 50% of participation with exclusion of patients with early progression decreasing the quality of the evidence. MTAC will re-review the technology once full data are analyzed. Conclusion: The interim analysis with less than 50% participation suggests that TTF plus Temozolomide may prolong progression-free survival and overall survival versus Temozolomide alone. Nevertheless, the study failed to include patients with severe prognosis, therefore results should be interpreted with cautious. Other pitfalls remain in the open-label nature of the RCT leading to placebo effects and variation in the delivery of chemotherapy and radiochemotherapy.
Articles: A literature search was conducted revealing 13 articles (Please refer to appendix B) of which one meets inclusion criteria (studies involving histologically confirmed GBM, standard concomitant chemoradiation with Temozolomide, age >18 years with ≥ 70% on Karnofsky Performance Status (KPS) score and good renal and bone marrow function, received TTFields plus Temozolomide as maintenance therapy). The study on "Maintenance Therapy with tumor-treating fields plus temozolomide vs Temozolomide alone for Glioblastoma: A randomized clinical trial" will be critically appraised.

The use of Tumor Treating Fields (TTFields) plus Temozolomide as maintenance therapy for Glioblastoma multiforme (GBM) does meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Date Created	Date Reviewed	Date Last Revised
10/01/2013	10/01/2013[MPC], 10/07/2014[MPC], 08/04/2015[MPC], 05/03/2016[MPC], 04/04/2017[MPC], 02/06/2018[MPC]	09/06/2016

[MPC] Medical Policy Committee

Revision History	Description
03/21/2016	Added MTAC Review for of Tumor Treating Fields (TTFields) plus Temozolomide as maintenance therapy for Glioblastoma multiforme (GBM)
05/03/2016	MPC approved GH developed criteria for Tumor Treating Fields (TTFields)
09/06/2016	Criteria added for continued treatment of TTF
06/28/2017	Added Medical Directors Comments
03/06/2018	MPC approved revised criteria for continued treatment of TTF

Codes

HCPCS: A4555; E0766

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LifeWise

MEDICAL POLICY – 1.01.29

Tumor Treating Fields Therapy for Glioblastoma

Effective Date:	Nov. 1, 2017	RELATED MEDICAL POLICIES:
Last Revised:	Oct. 3, 2017	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Tumor treating fields (TTF) is a new treatment being studied for use in certain cancers. The therapy consists of low-level electrical currents that arise from small insulated electrodes placed on the skin surface. TTF is believed to cause cell death during a later stage of development. Currently this therapy is covered as one treatment option for people who have a deadly form of brain cancer called glioblastoma multiforme. People wear a helmet with small electrodes attached to the scalp for at least 18 hours per day during TTF therapy. This treatment requires pre-approval by the plan, and this policy describes when this treatment is covered. TTF is considered investigational for other types of cancer (therefore not covered), as there is not yet enough scientific data that shows it works for other diagnoses.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Condition	Medical Necessity
Glioblastoma- adjuvant therapy	**Tumor treating fields (TTF) therapy to treat glioblastoma is medically necessary when ALL of the following are met:** • The patient has completed debulking surgery or biopsy **AND** • The patient has completed radiation therapy **AND** • The patient is being treated with temozolmide **AND** • TTF therapy is begun within 7 weeks of the final radiation treatment

Condition	Investigational
Glioblastoma- for advanced or recurrent disease	**Tumor treating fields therapy(TTF) to treat advanced or recurrent glioblastoma is considered investigational.**
All other diagnoses	**Tumor treating fields (TTF) is considered investigational for all other indications.**

Coding

Code	Description
HCPCS	
A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type

Related Information

N/A

Evidence Review

Background

Glioblastome Multiforme

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. They comprise approximately 15% of all brain and central nervous system tumors, and more than 50% of all tumors that arise from glial cells.[1] The peak incidence for GBM occurs between the ages of 45 and 70 years. GBMs are grade IV astrocytomas, the most deadly type of glial cell tumor, and are often resistant to standard chemotherapy.[1] According to the National Comprehensive Cancer Network, only a third of patients with GBM survive for 1 year and less than 5% live beyond 5 years.[2]

Treatment of Glioblastoma Multiforme

The primary treatment for initial GBM is debulking surgery to remove as much of the tumor as possible. At that time, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea, or BCNU) impregnated wafer.[2] Depending on the patient's physical condition, adjuvant radiotherapy and/or chemotherapy (typically temozolomide) are sometimes given. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide.

No standard treatment exists for recurrent GBM. After these initial treatments, additional debulking surgery may be used if recurrence is localized. Other treatment options for recurrent disease include various forms of systemic medications such as bevacizumab and bevacizumab combined with other chemotherapy such as irinotecan, BCNU/chloroethylnitrosourea (CCNU), or temozolomide. Temozolomide, nitrosourea, PCV (a combination of procarbazine, CCNU, and vincristine), cyclophosphamide, and platinum-based agents have also been used.[2] External beam radiotherapy also may be used. Response rates in recurrent disease are less than 10%, and progression-free survival at 6 months is typically less than 20%.[2,3]

Tumor Treating Fields Therapy

TTF therapy is a new, noninvasive technology intended to treat GBM on an outpatient basis using electrical fields.[3-5] TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. TTF are proposed to inhibit rapidly dividing tumor cells by two mechanisms: arrest of cell proliferation and destruction of cells while undergoing division.[4,5]

The NovoTTF-100A System has received marketing approval from the U.S. Food and Drug Administration to deliver TTF therapy. TTF therapy via the NovoTTF-100A System is delivered by a battery-powered, portable device that generates the fields via disposable electrodes noninvasively attached to the patient's shaved scalp over the site of the tumor.[3,4] The device is used by the patient at home on a continuous basis (20-24 h/d) for the duration of treatment, which can last for several months. The device is covered under the DME benefit. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.[3,4]

Summary of Evidence

For individuals who have progressive or recurrent glioblastoma multiforme (GBM) after initial or repeat surgery, radiotherapy, and/or chemotherapy who then receive tumor treatment fields (TTF) therapy as an alternative to standard chemotherapy, the evidence includes a randomized controlled trial (RCT) and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The published RCT reported no differences in outcomes between patients treated with TTF and with standard chemotherapy. This trial had several methodologic limitations. Comparisons that were made only included an active control of questionable efficacy, which might not reflect current standard of care. There was a high dropout rate (>20% of patients in each group were lost to follow-up) and, for the quality of life outcomes, only 25% of enrolled patients had complete data. The 2 nonrandomized studies were small and had limited validity due to differences in the patient populations treated with TTF and standard care. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have newly diagnosed GBM and receive TTF therapy as an adjunct to standard maintenance therapy following their initial treatment with surgery, radiotherapy, and/or chemotherapy, the evidence includes a single RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The single RCT reported that patients who received TTF treatment plus

temozolomide had longer progression-free survival (3.1 months) and overall survival (4.9 months) than patients who received temozolomide alone. However, the trial had methodologic limitations including the lack of a placebo control, differential dropout between groups, and the possibility of adherence bias for outcomes reported with per-protocol analysis. Further corroboration of these results is needed in high-quality RCTs. Although evidence is limited, NCCN has given this therapy a 2A rating. There are very few treatment options for this disease, and the side effect profile of TTF is much more tolerable to patients.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in **Table 1**.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01894061[a]	A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma	40	Dec 2017
NCT01756729[a]	A Prospective, Non-randomized, Concurrent Control, Open Label, Post-approval Study of NovoTTF-100A in Recurrent GBM Patient	486	Jan 2018
NCT02743078[a]	Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory Recurrent Glioblastoma	85	Apr 2018
NCT01954576	A Phase II Study of the NovoTTF-100A system, Enhanced by Genomic Analysis to Identify the Genetic Signature of Response in the Treatment of Recurrent Glioblastoma Multiforme	30	May 2018
NCT02663271[a]	A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma	25	May 2018
NCT02893137[a]	Phase 1 Enhancing Optune Therapy of Recurrent Glioblastoma Multiforme Using Targeted Surgical Skull Remodeling	15	Oct 2019

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT01925573[a]	Proposed Pilot Study of Combined Optune+ Bevacizumab, and Hypofractionated Stereotactic Irradiation for Bevacizumab-Naive Recurrent Glioblastoma	27	Dec 2021

NCT: national clinical trial. [a] Denotes industry-sponsored or cosponsored trial.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies (one of which provided 6 responses and 2 of which provided 1 response each) and 1 academic medical center (total of 9 individual responses) while this policy was under review in 2016. There was majority support, but not consensus, for use of tumor treatment fields therapy as an adjunct to maintenance treatment following initial therapy for glioblastoma multiforme. There was mixed support for the use of tumor treatment fields as an alternative to chemotherapy in advanced or recurrent glioblastoma multiforme.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2016)[2] include a recommendation for the treatment of glioblastoma. For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate MGMT promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric currents therapy is a category 2A recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a 2B recommendation.

Medicare National Coverage

There is no National Coverage Decision (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Status

In April 2011, the NovoTTF-100A™ System (Novocure, Haifa, Israel; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.[7] The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM [glioblastoma multiforme], following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."[7]

In September 2014, FDA approved Novocure's request to change its product name from NovoTTF-110A System to Optune®.[8]

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.[6] The device was granted priority review status in May 2015 because there was no legally marketed alternative device currently available for the treatment of newly diagnosed GBM that represents a life-threatening condition.

The FDA-approved label reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

Based on the 2011 approval Optune® is also approved for the treatment of recurrent GBM in the supratentorial region of the brain after receiving chemotherapy. The device is intended for use as a monotherapy, and as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

FDA product code: NZK.

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History

Date	Comments
10/14/13	New Policy. Policy created with literature search through June 3, 2013; considered investigational.

Date	Comments
12/06/13	Update Related Policies. Removed 8.01.31 as it was archived.
11/20/14	Annual Review. Policy updated with literature review through June 26, 2014. References 8 and 16-17 added. Editorial revisions made to rationale section. Policy statement unchanged. New HCPCS codes A9900 and E1399 added to the policy.
10/13/15	Annual Review. Policy updated with literature review through July 8, 2015; references10-11 removed and 10-12 added. Policy statement unchanged. Removed informational ICD-9 and ICD-10 codes.
09/01/16	Annual Review, approved August 9, 2016. Changed statement to MN when criteria are met.
03/30/17	Coding correction; updated code descriptions. Minor formatting update.
11/01/17	Annual Review, approved October 3, 2017. Policy updated with literature review through June 5, 2017; no references added. Removed HCPCS codes A9900 and E1399. Policy statements rewritten for clarity.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply.

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http://www.hhs.gov/ocr/office/file/index.html.

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This Notice has Important Information. This notice may have important information about your application or coverage through LifeWise Health Plan of Oregon. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-596-3440 (TTY: 800-842-5357).

አማሪኛ (Amharic):
ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ LifeWise Health Plan of Oregon ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀኖች ሊኖሩ ይችላሉ። የጤናን ሽፋንዎን ለመጠበቅና በአከፋፈል እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና ያለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መብት አለዎት።በስልክ ቁጥር 800-596-3440 (TTY: 800-842-5357) ይደውሉ።

العربية (Arabic):
يحوي هذا الإشعار معلومات هامة. قد يحوي هذا الإشعار معلومات مهمة بخصوص طلبك أو التغطية التي تريد الحصول عليها من خلال LifeWise Health Plan of Oregon. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تواريخ معينة للحفاظ على تغطيتك الصحية أو للمساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ(TTY: 800-842-5357) 800-596-3440

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 LifeWise Health Plan of Oregon 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-596-3440 (TTY: 800-842-5357)。

Oromoo (Cushite):
Beeksisni kun odeeffannoo barbaachisaa qaba. Beeksisti kun sagantaa yookan karaa LifeWise Health Plan of Oregon tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-596-3440 (TTY: 800-842-5357) tii bilbilaa.

Français (French):
Cet avis a d'importantes informations. Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de LifeWise Health Plan of Oregon. Le présent avis peut contenir des dates clés. Vous devrez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-596-3440 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè LifeWise Health Plan of Oregon. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resevwa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-596-3440 (TTY: 800-842-5357).

Deutsche (German):
Diese Benachrichtigung enthält wichtige Informationen. Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch LifeWise Health Plan of Oregon. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-596-3440 (TTY: 800-842-5357).

Hmoob (Hmong):
Tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntsiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam los ntawm LifeWise Health Plan of Oregon. Tej zaum muaj cov hnub tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyoog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-596-3440 (TTY: 800-842-5357).

Iloko (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti apliksayonyo wenno coverage babaen iti LifeWise Health Plan of Oregon. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-596-3440 (TTY: 800-842-5357).

Italiano (Italian):
Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso LifeWise Health Plan of Oregon. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiama 800-596-3440 (TTY: 800-842-5357).

037405 (07-2016)

日本語 (Japanese):
この通知には重要な情報が含まれています。この通知には、LifeWise Health Plan of Oregon の申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている可能性がある重要な日付をご確認ください。健康保険や有料サポートを維持するには、特定の期日までに行動を取らなければならない場合があります。ご希望の言語による情報とサポートが無料で提供されます。800-596-3440 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):
본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 LifeWise Health Plan of Oregon 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하는 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하는 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-596-3440 (TTY: 800-842-5357) 로 전화하십시오.

ລາວ (Lao):
ແຈ້ງການນີ້ມີຂໍ້ມູນສຳຄັນ. ແຈ້ງການນີ້ອາດຈະມີຂໍ້ມູນສຳຄັນກ່ຽວກັບຄຳຮ້ອງຂະໜັກ ຫຼື ຄວາມຄຸ້ມຄອງປະກັນໄພຂອງທ່ານຜ່ານ LifeWise Health Plan of Oregon. ອາດຈະມີວັນທີສຳຄັນໃນແຈ້ງການນີ້. ທ່ານອາດຈະຈຳເປັນຕ້ອງດຳເນີນການຕາມກຳນົດເວລາສະເພາະເພື່ອຮັກສາຄວາມຄຸ້ມຄອງປະກັນສຸຂະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເລື່ອງຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄວ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໂທຫາ 800-596-3440 (TTY: 800-842-5357).

ភាសាខ្មែរ (Khmer):
សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរ៉ាប់រងរបស់អ្នកតាមរយៈ LifeWise Health Plan of Oregon ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ចេញសមត្ថភាព ដល់កំណត់ថ្ងៃជាក់ច្បាស់នានា ដើម្បីនឹងរក្សាទុកការធានារ៉ាប់រងសុខភាពរបស់អ្នក ឬប្រាក់ជំនួយចេញថ្លៃ។ អ្នកមានសិទ្ធិទទួលព័ត៌មាននេះ និងជំនួយនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-596-3440 (TTY: 800-842-5357)។

ਪੰਜਾਬੀ (Punjabi):
ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ LifeWise Health Plan of Oregon ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਜਿਸ ਜਵਚ ਖਾਸ ਤਾਰੀਖਾ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀ ਜਸਹਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਛੁੱਕ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ਼ ਤੋਂ ਪਹਿਲਾਂ ਕੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫ਼ਤ ਵਿੱਚ ਤੇ ਆਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-596-3440 (TTY: 800-842-5357).

فارسی (Farsi):
این اعلامیه حاوی اطلاعات مهم میباشد .این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق LifeWise Health Plan of Oregon باشد. به تاریخ های مهم در این اعلامیه توجه نمایید .شما ممکن است برای حقظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید .شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-596-3440
(کاربران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

Polskie (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez LifeWise Health Plan of Oregon. Prosimy zwrócic uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-596-3440 (TTY: 800-842-5357).

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do LifeWise Health Plan of Oregon. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-596-3440 (TTY: 800-842-5357).

Română (Romanian):
Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastre de sănătate prin LifeWise Health Plan of Oregon. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența privitoare la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-596-3440 (TTY: 800-842-5357).

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через LifeWise Health Plan of Oregon. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-596-3440 (TTY: 800-842-5357).

Fa'asamoa (Samoan):
Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, LifeWise Health Plan of Oregon, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'matalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-596-3440 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de LifeWise Health Plan of Oregon. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-596-3440 (TTY: 800-842-5357).

Tagalog (Tagalog):
Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay maaaring naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng LifeWise Health Plan of Oregon. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-596-3440 (TTY: 800-842-5357).

ไทย (Thai):
ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับการการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน LifeWise Health Plan of Oregon และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-596-3440 (TTY: 800-842-5357)

Український (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через LifeWise Health Plan of Oregon. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-596-3440 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):
Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình LifeWise Health Plan of Oregon. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-596-3440 (TTY: 800-842-5357).

MEDICA®

UTILIZATION MANAGEMENT POLICY

TITLE: ELECTRIC TUMOR TREATMENT FIELDS

EFFECTIVE DATE: November 16, 2016

This policy was developed with input from specialists in neurosurgery, oncology, and radiation oncology and endorsed by the Medical Policy Committee.

IMPORTANT INFORMATION – PLEASE READ BEFORE USING THIS POLICY
These services may or may not be covered by all Medica plans. Please refer to the member's plan document for specific coverage information. If there is a difference between this general information and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid and MinnesotaCare members, this policy will apply unless these programs require different coverage. Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this Medica utilization management policy may call the Medica Provider Service Center toll-free at 1-800-458-5512.

Medica utilization management policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care and treatment.

PURPOSE
To promote consistency between reviewers in utilization management decision-making by providing the criteria that generally determine the medical necessity of electric tumor treatment fields (Optune System). The Coverage Issues box below outlines the process for addressing the needs of individuals who do not meet these criteria.

BACKGROUND
I. Definitions
   A. **Electric Tumor Treatment Fields (ETTF or TTF)** technology applies low-intensity alternating electric fields to the brain to disrupt the division of cancer cells. The Optune system (formerly known as NovoTTF-100A) consists of four sets of insulated electrodes and a generator. The array attaches to the patient's shaved scalp and is connected to the generator by wires. The patient wears the device continuously (20-24 hours per day), for at least four weeks.
   B. **Glioblastoma** also known as GBM, glioblastoma multiforme, and grade IV astrocytoma, is a fast-growing type of central nervous system tumor that forms from glial (supportive) tissue of the brain and spinal cord. Glioblastoma usually occurs in adults and affects the brain more often than the spinal cord. Symptoms depend on tumor location and may include language deficits, numbness, weakness, headaches, seizures, nausea and vomiting, or confusion. It is most common in older individuals, with a median survival rate of approximately 15 months; five-year survival rate is approximately 4%. The exact cause of glioblastoma is not known.
   C. The **NovoTAL simulation software** may be used to determine the optimal location for placement of the transducer array, which is based on the patient's MRI scan, head size, and tumor location.
   D. The **supratentorial** region of the brain is located above the tentorium cerebelli (the arched fold of dura mater that covers the upper surface of the cerebellum and supports the occipital lobes of the cerebrum) and contains the cerebrum.

MEDICAL NECESSITY CRITERIA
I. Indications for electric tumor treatment fields
   Documentation in the medical records indicates that **all of the following** criteria are met:
   A. The member is at least 22 years old
   B. There is histologically-confirmed glioblastoma multiforme (GBM)
   C. The treatment is being provided by a certified Novo-TTF 100A System prescriber, and **one of the following**

are met:
1. There is concurrent treatment of new disease with temozolomide (TMZ), unless TMZ has been ineffective, not tolerated, or is contraindicated, OR
2. There is recurrent disease and the treatment used as monotherapy after other options have been exhausted.

II. Contraindications

None of the following are present:

A. An active implantable medical device (e.g., deep brain stimulator, spinal cord stimulator, vagus nerve stimulator, pacemaker, defibrillator, programmable shunt)
B. Skull defect
C. Bullet fragment
D. Known sensitivity to conductive hydrogels used with device transducer arrays
E. Pregnancy.

COVERAGE ISSUES
1. Prior authorization **is required** for electric tumor treatment fields.
2. Coverage may vary according to the terms of the member's plan document.
3. Electric tumor treatment fields (Optune System) for all other indications, including the treatment of other malignant tumors, *is investigative, and therefore, not covered.*
4. For Medicare members, refer to the Medicare Coverage Database Search Page as applicable, at: http://www.cms.hhs.gov/mcd/search.asp?
5. If the Medical Necessity and Coverage Criteria are met, Medica will authorize benefits within the limits in the member's plan document.
6. If it appears that the Medical Necessity and Coverage Criteria are not met, the individual's case will be reviewed by the medical director or an external reviewer. Practitioners are reminded of the appeals process in their Medica Provider Administrative Manual.

DOCUMENT HISTORY

Original Effective Date	June 1, 2016
MPC Endorsement Date(s)	March 3, 2016, November 9, 2016

References:

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3. ECRI Institute. *ECRI Emerging Technology Evidence Report: Tumor Treating Fields Therapy (Optune) for Treating Recurrent Glioblastoma*. November 2015. Plymouth Meeting, PA.
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13. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma. A randomised phase III trial of a novel treatment modality. *Eur J Cancer.* September 2012;48(14):2192-2202. doi: 10.1016/j.ejca.2012.04.011.
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11/2015 MPC:

16. Batchelor T. Initial postoperative therapy for glioblastoma and anaplastic astrocytoma. Last updated August 2016. In: *UpToDate,* Basow, DS (Ed), UpToDate, Waltham, MA, 2016.
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Medi-Cal Update

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2. Updated Indications for HCPCS Code E0766

Effective for dates of service on or after February 1, 2016, the indications for the treatment of glioblastoma multiforme (GBM) with HCPCS code E0766 (electrical stimulation device used for cancer treatment, includes all accessories, any type) have been updated.

HCPCS code E0766 is indicated for the treatment of adult patients 22 years of age and older:

- With temozolomide for newly diagnosed, histologically confirmed supratentorial GBM following maximal debulking surgery, and completion of radiation therapy together with concomitant standard of care chemotherapy; or,
- With histologically or radiologically confirmed recurrent GBM in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy and an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

This information is reflected in the following provider manual(s):

Provider Manual(s)	Page(s) Updated
Durable Medical Equipment Pharmacy	dura bil dme (35)

Line: 1
Condition: PREGNANCY (See Guideline Notes 2,4,22,33,39,64,65,85,92,99,147,150,153,175)
Treatment: MATERNITY CARE
ICD-10: N88.3,O02.81-O02.89,O09.00-O09.A3,O09.211-O09.93,O10.011-O10.93,O11.1-O11.9,O12.00-O12.25,O13.1-O13.9,O14.00-O14.95,O15.00-O15.9,O16.1-O16.9,O20.0-O20.9,O21.0-O21.9,O22.00-O22.53,O22.8X1-O22.93,O23.00-O23.43,O23.511-O23.93,O24.011-O24.93,O25.10-O25.3,O26.00-O26.53,O26.611-O26.93,O29.011-O29.93,O30.001-O30.93,O31.00X0-O31.8X99,O32.0XX0-O32.9XX9,O33.0-O33.2,O33.3XX0-O33.9,O34.00-O34.13,O34.211-O34.93,O35.0XX0-O35.9XX9,O36.0110-O36.93X9,O40.1XX0-O40.9XX9,O41.00X0-O41.93X9,O42.00,O42.011-O42.92,O43.011-O43.93,O44.00-O44.53,O45.001-O45.93,O46.001-O46.93,O47.00-O47.9,O48.0-O48.1,O60.00-O60.03,O60.10X0-O60.23X9,O61.0-O61.9,O62.0-O62.9,O63.0-O63.9,O64.0XX0-O64.9XX9,O65.0-O65.9,O66.0-O66.3,O66.40-O66.9,O67.0-O67.9,O68,O69.0XX0-O69.9XX9,O70.0-O70.1,O70.20-O70.9,O71.00-O71.9,O72.0-O72.3,O73.0-O73.1,O74.0-O74.9,O75.0-O75.5,O75.81-O75.9,O76,O77.0-O77.9,O80-O85,O86.11-O86.89,O87.0-O87.9,O88.011-O88.83,O89.01-O89.9,O90.1-O90.6,O90.81-O90.9,O91.011-O91.03,O91.211-O91.23,O92.011-O92.79,O98.011-O98.93,O99.011-O99.89,O9A.111-O9A.53,Q92.61,Q95.0-Q95.1,Z03.71-Z03.79,Z22.330,Z29.13,Z31.82,Z32.00-Z32.02,Z34.00-Z34.93,Z36.0-Z36.5,Z36.81-Z36.9,Z3A.00-Z3A.49,Z39.0-Z39.2,Z86.32,Z87.51-Z87.59
CPT: 01958-01963,01967-01969,12021,12041,12042,13131-13133,37191-37193,57022,58150,58180,58260,58262,58290,58291,58541-58544,58550-58554,58559-58573,59000-59100,59160-59622,59866,59871,74712,74713,76801-76828,76945,76946,80081,81420,81507-81512,84163,84704,88235,88267,88269,93792,93793,96150-96155,97802-97814,98960-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0108,G0109,G0248-G0250,G0270,G0271,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,H0045,S2401-S2403,S2405,S2411,S8055,S9140,S9141,S9208-S9214

Line: 2
Condition: BIRTH OF INFANT (See Guideline Notes 64,65,153)
Treatment: NEWBORN CARE
ICD-10: P00.0-P00.7,P00.81-P00.9,P01.0-P01.9,P02.0-P02.1,P02.20-P02.9,P03.0-P03.6,P03.810-P03.9,P04.0-P04.3,P04.41-P04.9,P05.00-P05.9,P22.1,P29.11-P29.2,P29.4,P29.81-P29.9,P39.3,P92.01-P92.09,P94.1-P94.9,P96.0,P96.3-P96.5,P96.82-P96.89,Q27.0,Z05.0-Z05.3,Z05.41-Z05.9,Z38.00-Z38.8
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 3
Condition: PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS (See Coding Specification Below) (See Guideline Notes 1,17,64,65,106,122,140)
Treatment: MEDICAL THERAPY
ICD-10: Z00.00-Z00.01,Z00.110-Z00.5,Z00.70-Z00.8,Z01.00-Z01.10,Z01.110-Z01.118,Z01.411-Z01.42,Z08,Z11.1-Z11.4,Z11.51,Z12.11,Z12.2,Z12.31,Z12.4,Z13.1,Z13.220,Z13.4-Z13.6,Z13.820,Z13.88,Z20.1-Z20.7,Z20.810-Z20.89,Z23,Z29.11-Z29.12,Z29.14,Z29.8,Z39.1,Z71.41,Z71.7,Z76.1-Z76.2,Z80.0,Z80.41,Z91.81
CPT: 44392,44394,45333,45338,45384,45385,76706,77067,90378,90460-90472,90620,90621,90630-90674,90680-90688,90696-90716,90723-90736,90739-90748,90750,90756,92002-92014,92551,93792,93793,96110,96150-96155,98966-98969,99051,99060,99070,99078,99173,99188,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: D0191,D1206,G0008-G0010,G0104,G0105,G0121,G0248-G0250,G0296,G0297,G0396,G0397,G0438-G0445,G0463-G0468,G0490,G0511,G0513,G0514,H0049,H0050,S0285,S0610-S0613,S9443

CPT code 96110 can be billed in addition to other CPT codes, such as evaluation and management (E&M) codes or preventive visit codes.

Line: 4
Condition: SUBSTANCE USE DISORDER (See Guideline Notes 64,65,175)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F10.10-F10.11,F10.20-F10.21,F11.10-F11.11,F11.20-F11.21,F12.10-F12.11,F12.20-F12.21,F13.10-F13.11,F13.20-F13.21,F14.10-F14.11,F14.20-F14.21,F15.10-F15.11,F15.20-F15.21,F16.10-F16.11,F16.20-F16.21,F18.10-F18.11,F18.20-F18.21,F19.10-F19.11,F19.20-F19.21,Z71.51
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,96150-96155,97810-97814,98966-98969,99051,99060,99201-99239,99324-99357,99366,99408,99409,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0410,G0411,G0425-G0427,G0443,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004-H0006,H0010-H0016,H0018-H0020,H0032-H0035,H0038,H2010,H2013,H2033,H2035,T1006,T1007,T1502

Line: **5**
Condition: TOBACCO DEPENDENCE (See Guideline Notes 4,64,65,92)
Treatment: MEDICAL THERAPY/BEHAVIORAL COUNSELING
ICD-10: F17.200-F17.228,F17.290-F17.299,Z71.6,Z72.0
CPT: 93792,93793,96150-96155,97810-97814,98966-98969,99078,99201-99215,99224,99324-99355,99366,99406,99407,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: D1320,G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,G9016,H0038,S9453

Line: **6**
Condition: REPRODUCTIVE SERVICES (See Guideline Notes 64,65,68,162,176)
Treatment: CONTRACEPTION MANAGEMENT; STERILIZATION
ICD-10: Z30.011-Z30.9,Z31.61-Z31.69,Z39.2,Z40.03
CPT: 11976,11981-11983,55250,57170,58300,58301,58340,58565,58600-58615,58661,58670,58671,58700,74740,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S4981,S4989,T1015

Line: **7**
Condition: MAJOR DEPRESSION, RECURRENT; MAJOR DEPRESSION, SINGLE EPISODE, SEVERE (See Guideline Notes 64,65,69,102)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F32.2-F32.5,F32.9,F33.0-F33.3,F33.40-F33.42,F33.9
CPT: 90785,90832-90840,90846-90853,90867,90868,90870,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99281-99285,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005

Line: **8**
Condition: TYPE 1 DIABETES MELLITUS (See Coding Specification Below) (See Guideline Notes 62,64,65,108)
Treatment: MEDICAL THERAPY
ICD-10: E10.10-E10.29,E10.311-E10.319,E10.3211-E10.9,E89.1,O24.011-O24.019,Z46.81
CPT: 49435,49436,90935-90947,90989-90997,92002-92014,92227,92250,93792,93793,95249-95251,96150-96155,97605-97608,97802-97804,98960-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0108,G0109,G0245,G0246,G0248-G0250,G0270,G0271,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9140-S9145,S9353

CPT 95250 and 95251 are included on this line for services related to real-time continuous glucose monitoring but not retrospective (professional) continuous glucose monitoring.

Line: **9**
Condition: ASTHMA (See Guideline Notes 64,65,156)
Treatment: MEDICAL THERAPY
ICD-10: J45.20-J45.52,J45.901-J45.998,Z51.6
CPT: 31600,31601,31820,31825,86003,86008,86486,93792,93793,94002-94005,94640,94644-94668,95004,95018-95180,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0424-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9441

Line: **10**
Condition: GALACTOSEMIA (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: E74.20-E74.29
CPT: 93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 11
Condition: RESPIRATORY CONDITIONS OF FETUS AND NEWBORN (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: P22.0,P22.8-P22.9,P23.0-P23.9,P24.00-P24.9,P25.0-P25.8,P26.0-P26.9,P28.0,P28.10-P28.9,P84,Q31.0,R04.81
CPT: 31580,33946-33966,33969,33984-33989,39501,39503,39545,93792,93793,94002-94005,94610,94640,94660-94668,94772-94777,96154,96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 12
Condition: HIV DISEASE (INCLUDING ACQUIRED IMMUNODEFICIENCY SYNDROME) AND RELATED OPPORTUNISTIC INFECTIONS (See Guideline Notes 7,64,65)
Treatment: MEDICAL THERAPY
ICD-10: B20,Z21
CPT: 90284,93792,93793,94642,96150-96155,97810-97814,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 13
Condition: CONGENITAL HYPOTHYROIDISM (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: E00.0-E00.9,E03.0-E03.1,P72.0
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 14
Condition: PHENYLKETONURIA (PKU) (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: E70.0-E70.1
CPT: 93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 15
Condition: CONGENITAL INFECTIOUS DISEASES (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A50.01-A50.9,P35.0-P35.9,P37.0-P37.4,P37.8-P37.9
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 16
Condition: LOW BIRTH WEIGHT; PREMATURE NEWBORN (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: P07.00-P07.39,P83.0,P91.60
CPT: 92227,92228,93792,93793,94772,96154,96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 17
Condition: NEONATAL MYASTHENIA GRAVIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: P94.0
CPT: 93792,93793,96154,96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 18
Condition: FEEDING PROBLEMS IN NEWBORNS (See Guideline Notes 64,65,139)
Treatment: MEDICAL THERAPY
ICD-10: P78.2,P78.83,P92.1-P92.9,Q38.1
CPT: 41010,92526,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: D7960,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **19**
Condition: HYDROCEPHALUS AND BENIGN INTRACRANIAL HYPERTENSION (See Guideline Note 65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: G91.0-G91.3,G91.8-G91.9,G93.2,Q03.0-Q03.9,Q04.4-Q04.8,Q05.0-Q05.3,Q07.02-Q07.03,Z45.41
CPT: 20664,31294,61020,61070,61107,61120,61210,61215,61322,61323,62100,62120,62121,62160-62163,62180-62258,62272,63740-63746,67570,92002-92014,92081-92083,92133,92134,92226,92250,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **20**
Condition: CYSTIC FIBROSIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: E84.0,E84.11-E84.9
CPT: 31600,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **21**
Condition: VESICOURETERAL REFLUX (See Guideline Notes 64,65,138)
Treatment: MEDICAL THERAPY, SURGERY
ICD-10: N13.70-N13.71,N13.721-N13.9,Q62.7
CPT: 50220,50225,50234-50240,50605,50760-50820,50845,50860,50947,50948,52281,52327,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **22**
Condition: SCHIZOPHRENIC DISORDERS (See Guideline Notes 64,65,69,82)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F20.0-F20.5,F20.81-F20.9,F25.0-F25.9
CPT: 90785,90832-90840,90846-90853,90870,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99281-99285,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005

Line: **23**
Condition: INTRACRANIAL HEMORRHAGES; CEREBRAL CONVULSIONS, DEPRESSION, COMA, AND OTHER ABNORMAL CERERAL SIGNS OF THE NEWBORN (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: P90,P91.0-P91.1,P91.3-P91.5,P91.811-P91.9
CPT: 93792,93793,96154,96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **24**
Condition: ENDOCRINE AND METABOLIC DISTURBANCES SPECIFIC TO THE FETUS AND NEWBORN (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: P70.0-P70.9,P71.0-P71.9,P72.1-P72.9,P74.0-P74.9
CPT: 93792,93793,96154,96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **25**
Condition: DYSPLASIA OF CERVIX AND CERVICAL CARCINOMA IN SITU, CERVICAL CONDYLOMA (See Guideline Notes 64,65,66)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: D06.0-D06.9,N84.2,N86,N87.0-N87.9,N88.0,N89.0-N89.4,R87.610-R87.616,R87.810,R87.820,Z87.410
CPT: 57061,57065,57150,57180,57400,57452-57530,57540,57550-57558,58120,58150,58260-58263,58290,58291,58550-58554,58570-58573,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **26**
Condition: BIPOLAR DISORDERS (See Guideline Notes 64,65,69,82)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F30.10-F30.9,F31.0,F31.10-F31.9
CPT: 90785,90832-90840,90846-90853,90870,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239, 99281-99285,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470, G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,S9537,T1005

Line: **27**
Condition: TYPE 2 DIABETES MELLITUS (See Guideline Notes 62,64,65)
Treatment: MEDICAL THERAPY
ICD-10: E08.00-E08.29,E08.311-E08.319,E08.3211-E08.9,E09.00-E09.29,E09.311-E09.319,E09.3211-E09.9,E11.00-E11.29,E11.311-E11.319,E11.3211-E11.9,E13.00-E13.29,E13.311-E13.319,E13.3211-E13.9,E16.1
CPT: 48155,90935-90947,90989-90997,92002-92014,92227,92250,93792,93793,96150-96155,97605-97608,97802-97804,98960-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449, 99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0108,G0109,G0245,G0246,G0248-G0250,G0270,G0271,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9140-S9145,S9353,S9537

Line: **28**
Condition: DRUG WITHDRAWAL SYNDROME IN NEWBORN (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: P96.1-P96.2
CPT: 93792,93793,96154,96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **29**
Condition: REGIONAL ENTERITIS, IDIOPATHIC PROCTOCOLITIS, ULCERATION OF INTESTINE (See Guideline Notes 9,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: K50.00,K50.011-K50.919,K51.00,K51.011-K51.319,K51.411-K51.413,K51.418-K51.919,K52.3,K62.6,K63.2-K63.3, K92.81,Z46.59
CPT: 44110,44120-44125,44139-44160,44187-44227,44300-44320,44345,44379,44381,44384,44391,44402,44404, 44405,44620-44661,44701,45112-45119,45123,45136,45303,45308-45320,45327,45334,45335,45340,45347, 45381,45382,45386,45389,45397,45805,45825,46710,46712,49442,86711,91110,93792,93793,96150-96155, 97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **30**
Condition: EPILEPSY AND FEBRILE CONVULSIONS (See Guideline Notes 64,65,84)
Treatment: MEDICAL THERAPY
ICD-10: G40.001-G40.919,R56.00-R56.9
CPT: 93792,93793,96150-96155,97535,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239, 99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **31**
Condition: SEVERE BIRTH TRAUMA FOR BABY; INTRAVENTRICULAR HEMORRHAGE (See Guideline Notes 6,64,65)
Treatment: MEDICAL THERAPY
ICD-10: P10.0-P10.9,P11.0,P11.2,P11.5-P11.9,P12.2,P19.0-P19.9,P52.0-P52.1,P52.21-P52.9
CPT: 93792,93793,96154,96155,97110-97124,97140-97168,97530,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **32**
Condition: HEMATOLOGICAL DISORDERS OF FETUS AND NEWBORN (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: P53,P60,P61.0,P61.6
CPT: 93792,93793,96154,96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 33
Condition: SPINA BIFIDA (See Guideline Notes 64,65)
Treatment: SURGICAL TREATMENT
ICD-10: Q05.0-Q05.9,Q07.00-Q07.03
CPT: 27036,61070,61343,62160,62180-62258,63700-63710,93792,93793,96150-96155,98966-98969,99051,99060, 99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 34
Condition: OTHER CONGENITAL ANOMALIES OF MUSCULOSKELETAL SYSTEM (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: Q79.0-Q79.4,Q79.51-Q79.59
CPT: 39503,39545,49600-49611,51500,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239, 99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 35
Condition: TERMINATION OF PREGNANCY (See Guideline Notes 64,65,99) (Note: This line item is not priced as part of the list)
Treatment: INDUCED ABORTION
ICD-10: A34,O02.89,O03.87,O04.5-O04.7,O04.80-O04.89,O07.0-O07.2,O07.30-O07.4,O08.0-O08.7,O08.81-O08.9, O35.0XX0-O35.6XX9,O35.8XX0-O35.9XX9,O36.80X0-O36.8199,Z30.8,Z33.2,Z3A.00-Z3A.22
CPT: 01966,58520,59100,59160,59200,59812,59830-59857,76801-76810,76815-76817,93792,93793,96150-96155, 98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, S0199,S2260

Line: 36
Condition: ACQUIRED HYPOTHYROIDISM, DYSHORMONOGENIC GOITER (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: E01.8,E02,E03.2-E03.9,E07.1,E89.0
CPT: 60210-60240,60270,60271,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 37
Condition: ECTOPIC PREGNANCY; HYDATIDIFORM MOLE; CHORIOCARCINOMA (See Guideline Notes 64,65,99)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: C58,O00.00-O00.01,O00.101-O00.91,O01.0-O01.9,Z87.59
CPT: 32553,49327,49411,49412,57020,58120,58150,58180,58200,58260,58520,58541-58544,58550-58554,58570-58573,58660-58662,58673,58700-58740,58770,58940,58953,58956,59100-59151,59870,76801-76810,76815-76817,77014,77261-77290,77295,77300,77321-77370,77387,77401-77417,77424-77427,77469,77470,93792, 93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060, 99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 38
Condition: PRIMARY AND SECONDARY SYPHILIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A51.0-A51.2,A51.31-A51.9,A52.00-A52.09
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 39
Condition: DISORDERS RELATING TO LONG GESTATION AND HIGH BIRTHWEIGHT (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: P08.0-P08.1,P08.21-P08.22
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **40**
Condition: PANHYPOPITUITARISM, IATROGENIC AND OTHER PITUITARY DISORDERS (See Guideline Notes 64,65,74)
Treatment: MEDICAL THERAPY
ICD-10: E23.0-E23.1,E23.6,E24.1,E89.3
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **41**
Condition: INTUSSCEPTION, VOLVULUS, INTESTINAL OBSTRUCTION, HAZARDOUS FOREIGN BODY IN GI TRACT WITH RISK OF PERFORATION OR OBSTRUCTION (See Guideline Notes 64,65,128)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: K31.5,K51.012,K51.212,K51.312,K51.412,K51.512,K51.812,K51.912,K56.1-K56.2,K56.41-K56.52,K56.600-K56.699,K59.31-K59.39,T18.2XXA-T18.2XXD,T18.3XXA-T18.3XXD,T18.4XXA-T18.4XXD,T18.5XXA-T18.5XXD,T18.8XXA-T18.8XXD,T18.9XXA-T18.9XXD,Z46.59
CPT: 43241,43247,43500,43870,44005,44010,44020-44055,44110-44130,44139-44213,44300,44310,44320,44370,44379,44381,44384,44390,44392-44402,44404,44405,44408,44615,44625,44626,44701,45303,45307-45315,45320-45327,45332,45333,45335-45340,45346,45347,45379,45381,45384-45389,45393,45915,46604,46608,49402,49442,74283,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **42**
Condition: CLEFT PALATE WITH AIRWAY OBSTRUCTION (See Guideline Notes 36,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, ORTHODONTICS
ICD-10: J39.8,J98.09,Q31.0-Q31.9,Q32.0-Q32.4,Q35.1-Q35.9
CPT: 30140,30520,30620,31527,31545-31561,31587,31630,31631,31636-31638,31641,31780,31781,31820,33800,41510,42820-42836,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: D8010-D8040,D8070-D8694,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **43**
Condition: NEONATAL INFECTIONS OTHER THAN SEPSIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: P38.1-P38.9,P39.0,P39.3-P39.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **44**
Condition: COARCTATION OF THE AORTA (See Guideline Note 65)
Treatment: SURGICAL TREATMENT
ICD-10: Q25.1,Q25.29,Q25.40-Q25.42,Q25.45-Q25.46,Q25.48-Q25.49,Q25.8-Q25.9
CPT: 33720,33722,33802,33803,33840-33853,33946-33966,33969,33984-33989,37246,37247,75557-75561,75565,92960-92971,92978-92998,93355,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **45**
Condition: CORONARY ARTERY ANOMALY (See Guideline Note 65)
Treatment: REIMPLANTATION OF CORONARY ARTERY
ICD-10: Q24.5
CPT: 33500-33510,33530,35572,92920-92938,92943,92944,92960-92998,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **46**
Condition: RHEUMATOID ARTHRITIS AND OTHER INFLAMMATORY POLYARTHROPATHIES (See Guideline Notes 6,64,65)
Treatment: MEDICAL THERAPY, INJECTIONS
ICD-10: A39.84,L40.50-L40.59,M02.011-M02.19,M02.211-M02.89,M05.00,M05.011-M05.9,M06.00,M06.011-M06.29, M06.38,M06.4,M06.80,M06.811-M06.9,M08.00,M08.011-M08.99,M14.811-M14.89
CPT: 20550,20600-20611,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98925-98942,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404, 99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513,G0514

Line: **47**
Condition: DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS (See Guideline Notes 36,62,64,65,100)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: A06.4-A06.6,A54.82,D73.3,E32.1,G06.0-G06.2,G07-G08,H05.011-H05.049,J36,J39.0-J39.1,J85.0-J85.3,J86.0-J86.9,K35.2-K35.3,K35.80-K35.89,K36-K37,K38.0-K38.8,K50.014,K50.114,K50.814,K50.914,K51.014,K51.214, K51.314,K51.414,K51.514,K51.814,K51.914,K57.00-K57.01,K57.20-K57.21,K57.40-K57.41,K57.80-K57.81,K63.0-K63.1,K65.0-K65.1,K65.3-K65.9,K68.12-K68.19,K75.0-K75.1,M46.30-M46.39,M65.00,M65.011-M65.08,M67.20, M67.211-M67.29,M71.00,M71.011-M71.09,M71.80,M71.811-M71.89,N10,N15.1,N28.84-N28.86,N49.3,O91.111-O91.13,P78.0
CPT: 10030,10060,10061,10160,10180,19020,20930-20938,22010,22015,22532-22632,22840-22855,22859,23031, 23405,23406,23930,25000,25031,25085,25118,26020-26034,26990,27301,27603,28001,31610,31612,31613, 31645,31646,32035,32036,32200-32320,32480-32488,32550,32552,32554-32562,32650-32652,32655,32656, 32663-32665,32810,32815,32906,32940,33015-33050,37212,38100-38120,39000,39010,39220,42700-42725, 42808-42972,43840,44120-44125,44130,44139-44160,44187-44227,44300-44316,44602-44605,44620-44626, 44900-44970,45000,47010,47015,48140-48154,49020,49322,49405-49407,49422,49423,50020,50220,50391, 50400,50405,50520-50526,50542-50546,50548,50575,50693-50695,50947,50948,52332,52334,61105-61253, 61312-61323,61501,61514,61522,61570,61571,61582,61600,62140-62160,62163,62268,63045-63048,63075-63091,63265-63273,63295,67405,67414,67445,68400,75984,92002-92014,93792,93793,96150-96155,97605-97608,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449, 99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **48**
Condition: CHRONIC RESPIRATORY DISEASE ARISING IN THE NEONATAL PERIOD (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: P27.0-P27.9
CPT: 31601,31820,31825,93792,93793,94774-94777,96150-96155,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **49**
Condition: CONGENITAL HYDRONEPHROSIS (See Guideline Notes 64,65)
Treatment: NEPHRECTOMY/REPAIR
ICD-10: Q62.0,Q62.10-Q62.39
CPT: 50100,50220-50240,50400,50405,50500,50540,50544,50546,50553,50572,50575,50600,50605,50693-50695, 50722-50728,50760,50780-50785,50845-50900,50970,51535,52290-52301,52310,52334-52346,52352-52354, 52356,52400,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **50**
Condition: PULMONARY TUBERCULOSIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A15.0-A15.9,A19.0-A19.9,A31.0
CPT: 32662,32906,32960,33015-33050,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **51**
Condition: ACUTE PELVIC INFLAMMATORY DISEASE (See Guideline Notes 64,65,110)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: A18.17,A56.11,N70.01-N70.03,N70.91-N70.93,N71.0,N71.9,N73.0,N73.2-N73.5,N73.8-N73.9,N74
CPT: 44960,57010,58150-58200,58260-58294,58541-58544,58550-58554,58570-58573,58660-58662,58700-58740, 58820,58822,58925,58940,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **52**
Condition: GONOCOCCAL INFECTIONS AND OTHER SEXUALLY TRANSMITTED DISEASES OF THE ORAL, ANAL AND GENITOURINARY TRACT (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A54.00-A54.29,A54.40-A54.81,A54.83,A54.85,A54.89-A54.9,A55,A56.00-A56.8,A57-A58,A60.00-A60.9,A63.8, A64,A74.81-A74.9,N34.1
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **53**
Condition: PREVENTIVE DENTAL SERVICES (See Guideline Notes 17,64,65)
Treatment: CLEANING, FLUORIDE AND SEALANTS
ICD-10: K00.4,K08.55,Z01.20-Z01.21,Z29.3,Z91.841-Z91.849
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99188,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: D0120,D0145,D0150,D0180,D0191,D0601-D0603,D1110-D1310,D1330,D1351,D1510-D1575,D4346,D4355, D5986,D9920,G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **54**
Condition: DENTAL CONDITIONS (E.G., INFECTION, PAIN, TRAUMA)
Treatment: EMERGENCY DENTAL SERVICES
ICD-10: S02.5XXA-S02.5XXB,S03.2XXA-S03.2XXD
HCPCS: D0140,D0160,D0170,D3110,D3221,D7140,D7210,D7260-D7270,D7510,D7520,D7530,D7560,D7670,D7770, D7910,D7911,D7997,D9110,D9410,D9420,D9440,D9610,D9612,D9995,D9996

Line: **55**
Condition: COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS (See Coding Specification Below) (See Guideline Notes 64,65,167)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: K56.3,K80.00-K80.19,K80.21-K80.47,K80.51-K80.67,K80.71,K80.81,K81.0-K81.9,K82.0-K82.3,K82.8,K83.0-K83.3
CPT: 43260-43265,43273-43278,47015,47420-47490,47533-47540,47542,47544,47554-47620,47701-47900,48548, 49422,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404, 99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

ICD-10 K82.8 (Other specified diseases of gallbladder) is included on Line 55 when the patient has porcelain gallbladder or gallbladder dyskinesia with a gallbladder ejection fraction <35%. Otherwise, K82.8 is included on Line 639.

Line: **56**
Condition: ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE (See Guideline Notes 9,64,65,77)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: I85.00-I85.11,I86.4,K22.11,K22.6,K22.8,K25.0-K25.9,K26.0-K26.9,K27.0-K27.9,K28.0-K28.9,K29.00-K29.91, K31.1,K31.3,K31.5,K31.811-K31.82,K52.0,K55.20-K55.21,K57.11,K57.31,K57.51,K57.91,K62.5,K63.81,K92.2, P54.1-P54.3,P78.82
CPT: 37145,37160,37181-37183,37244,38100,43107-43124,43192,43201,43204,43205,43210,43227,43241,43243-43245,43255,43270,43280,43286-43288,43327,43328,43400,43401,43410,43415,43460,43501,43502,43520, 43610-43641,43800,43820,43825,43840,43850,43855,43865,43870,44160,44186,44320,44391-44401,44404, 44602,44603,44620-44626,45308-45320,45333-45335,45346,45381-45384,45388,46614,64680,65778-65782, 68371,77014,91110,93792,93793,96150-96155,96900,96902,96910-96913,98966-98969,99051,99060,99070, 99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498, 99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **57**
Condition: BURN, FULL THICKNESS GREATER THAN 10% OF BODY SURFACE (See Guideline Notes 6,64,65)
Treatment: FREE SKIN GRAFT, MEDICAL THERAPY
ICD-10: L00,L49.7,T20.30XA-T20.30XD,T20.311A-T20.311D,T20.312A-T20.312D,T20.319A-T20.319D,T20.32XA-T20.32XD,T20.33XA-T20.33XD,T20.34XA-T20.34XD,T20.35XA-T20.35XD,T20.36XA-T20.36XD,T20.37XA-T20.37XD,T20.39XA-T20.39XD,T20.70XA-T20.70XD,T20.711A-T20.711D,T20.712A-T20.712D,T20.719A-T20.719D,T20.72XA-T20.72XD,T20.73XA-T20.73XD,T20.74XA-T20.74XD,T20.75XA-T20.75XD,T20.76XA-T20.76XD,T20.77XA-T20.77XD,T20.79XA-T20.79XD,T21.30XA-T21.30XD,T21.31XA-T21.31XD,T21.32XA-T21.32XD,T21.33XA-T21.33XD,T21.34XA-T21.34XD,T21.35XA-T21.35XD,T21.36XA-T21.36XD,T21.37XA-T21.37XD,T21.39XA-T21.39XD,T21.70XA-T21.70XD,T21.71XA-T21.71XD,T21.72XA-T21.72XD,T21.73XA-T21.73XD,T21.74XA-T21.74XD,T21.75XA-T21.75XD,T21.76XA-T21.76XD,T21.77XA-T21.77XD,T21.79XA-T21.79XD,T22.30XA-T22.30XD,T22.311A-T22.311D,T22.312A-T22.312D,T22.319A-T22.319D,T22.321A-T22.321D,T22.322A-T22.322D,T22.329A-T22.329D,T22.331A-T22.331D,T22.332A-T22.332D,T22.339A-T22.339D,T22.341A-T22.341D,T22.342A-T22.342D,T22.349A-T22.349D,T22.351A-T22.351D,T22.352A-

T22.352D,T22.359A-T22.359D,T22.361A-T22.361D,T22.362A-T22.362D,T22.369A-T22.369D,T22.391A-T22.391D,T22.392A-T22.392D,T22.399A-T22.399D,T22.70XA-T22.70XD,T22.711A-T22.711D,T22.712A-T22.712D,T22.719A-T22.719D,T22.721A-T22.721D,T22.722A-T22.722D,T22.729A-T22.729D,T22.731A-T22.731D,T22.732A-T22.732D,T22.739A-T22.739D,T22.741A-T22.741D,T22.742A-T22.742D,T22.749A-T22.749D,T22.751A-T22.751D,T22.752A-T22.752D,T22.759A-T22.759D,T22.761A-T22.761D,T22.762A-T22.762D,T22.769A-T22.769D,T22.791A-T22.791D,T22.792A-T22.792D,T22.799A-T22.799D,T23.301A-T23.301D,T23.302A-T23.302D,T23.309A-T23.309D,T23.311A-T23.311D,T23.312A-T23.312D,T23.319A-T23.319D,T23.321A-T23.321D,T23.322A-T23.322D,T23.329A-T23.329D,T23.331A-T23.331D,T23.332A-T23.332D,T23.339A-T23.339D,T23.341A-T23.341D,T23.342A-T23.342D,T23.349A-T23.349D,T23.351A-T23.351D,T23.352A-T23.352D,T23.359A-T23.359D,T23.361A-T23.361D,T23.362A-T23.362D,T23.369A-T23.369D,T23.371A-T23.371D,T23.372A-T23.372D,T23.379A-T23.379D,T23.391A-T23.391D,T23.392A-T23.392D,T23.399A-T23.399D,T23.701A-T23.701D,T23.702A-T23.702D,T23.709A-T23.709D,T23.711A-T23.711D,T23.712A-T23.712D,T23.719A-T23.719D,T23.721A-T23.721D,T23.722A-T23.722D,T23.729A-T23.729D,T23.731A-T23.731D,T23.732A-T23.732D,T23.739A-T23.739D,T23.741A-T23.741D,T23.742A-T23.742D,T23.749A-T23.749D,T23.751A-T23.751D,T23.752A-T23.752D,T23.759A-T23.759D,T23.761A-T23.761D,T23.762A-T23.762D,T23.769A-T23.769D,T23.771A-T23.771D,T23.772A-T23.772D,T23.779A-T23.779D,T23.791A-T23.791D,T23.792A-T23.792D,T23.799A-T23.799D,T24.301A-T24.301D,T24.302A-T24.302D,T24.309A-T24.309D,T24.311A-T24.311D,T24.312A-T24.312D,T24.319A-T24.319D,T24.321A-T24.321D,T24.322A-T24.322D,T24.329A-T24.329D,T24.331A-T24.331D,T24.332A-T24.332D,T24.339A-T24.339D,T24.391A-T24.391D,T24.392A-T24.392D,T24.399A-T24.399D,T24.701A-T24.701D,T24.702A-T24.702D,T24.709A-T24.709D,T24.711A-T24.711D,T24.712A-T24.712D,T24.719A-T24.719D,T24.721A-T24.721D,T24.722A-T24.722D,T24.729A-T24.729D,T24.731A-T24.731D,T24.732A-T24.732D,T24.739A-T24.739D,T24.791A-T24.791D,T24.792A-T24.792D,T24.799A-T24.799D,T25.311A-T25.311D,T25.312A-T25.312D,T25.319A-T25.319D,T25.321A-T25.321D,T25.322A-T25.322D,T25.329A-T25.329D,T25.331A-T25.331D,T25.332A-T25.332D,T25.339A-T25.339D,T25.391A-T25.391D,T25.392A-T25.392D,T25.399A-T25.399D,T25.711A-T25.711D,T25.712A-T25.712D,T25.719A-T25.719D,T25.721A-T25.721D,T25.722A-T25.722D,T25.729A-T25.729D,T25.731A-T25.731D,T25.732A-T25.732D,T25.739A-T25.739D,T25.791A-T25.791D,T25.792A-T25.792D,T25.799A-T25.799D,T26.00XA-T26.00XD,T26.01XA-T26.01XD,T26.02XA-T26.02XD,T26.10XA-T26.10XD,T26.11XA-T26.11XD,T26.12XA-T26.12XD,T26.20XA-T26.20XD,T26.21XA-T26.21XD,T26.22XA-T26.22XD,T26.30XA-T26.30XD,T26.31XA-T26.31XD,T26.32XA-T26.32XD,T26.40XA-T26.40XD,T26.41XA-T26.41XD,T26.42XA-T26.42XD,T26.50XA-T26.50XD,T26.51XA-T26.51XD,T26.52XA-T26.52XD,T26.60XA-T26.60XD,T26.61XA-T26.61XD,T26.62XA-T26.62XD,T26.70XA-T26.70XD,T26.71XA-T26.71XD,T26.72XA-T26.72XD,T26.80XA-T26.80XD,T26.81XA-T26.81XD,T26.82XA-T26.82XD,T26.90XA-T26.90XD,T26.91XA-T26.91XD,T26.92XA-T26.92XD,T27.0XXA-T27.0XXD,T27.1XXA-T27.1XXD,T27.2XXA-T27.2XXD,T27.3XXA-T27.3XXD,T27.4XXA-T27.4XXD,T27.5XXA-T27.5XXD,T27.6XXA-T27.6XXD,T27.7XXA-T27.7XXD,T28.0XXA-T28.0XXD,T28.1XXA-T28.1XXD,T28.2XXA-T28.2XXD,T28.3XXA-T28.3XXD,T28.40XA-T28.40XD,T28.411A-T28.411D,T28.412A-T28.412D,T28.419A-T28.419D,T28.49XA-T28.49XD,T28.5XXA-T28.5XXD,T28.6XXA-T28.6XXD,T28.7XXA-T28.7XXD,T28.8XXA-T28.8XXD,T28.90XA-T28.90XD,T28.911A-T28.911D,T28.912A-T28.912D,T28.919A-T28.919D,T28.99XA-T28.99XD,T31.11,T31.21-T31.22,T31.31-T31.33,T31.41-T31.44,T31.51-T31.55,T31.61-T31.66,T31.71-T31.77,T31.81-T31.88,T31.91-T31.99,T32.11,T32.21-T32.22,T32.31-T32.33,T32.41-T32.44,T32.51-T32.55,T32.61-T32.66,T32.71-T32.77,T32.81-T32.88,T32.91-T32.99

CPT: 11000,11042,11045,11960-11971,15002-15005,15271-15278,16000-16036,25900-25931,26910-26952,27888,28800-28825,65778-65782,68371,92002-92014,92507,92508,92521-92524,92607-92609,92633,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9152

Line: **58**
Condition: BRONCHIECTASIS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: J47.0-J47.9,J98.09
CPT: 31645,31646,32320,32480-32488,32501,32505-32507,32663,32666-32670,93792,93793,94002-94005,94640,94660-94668,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0424-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **59**
Condition: END STAGE RENAL DISEASE (See Guideline Notes 7,64,65)
Treatment: MEDICAL THERAPY INCLUDING DIALYSIS
ICD-10: E08.21-E08.29,E09.21-E09.29,E10.21-E10.29,E11.21-E11.29,E13.21-E13.29,M32.14-M32.15,M35.04,N05.0-N05.1,N18.6
CPT: 36818-36821,36831-36838,36901-36909,49324-49326,49421,49422,49435,49436,90935-90997,93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0420,G0421,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9339,S9537

Line: **60**
Condition: METABOLIC DISORDERS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: D81.810,D84.1,E71.310-E71.548,E75.00-E75.09,E75.11-E75.22;E75.240-E75.249,E75.3-E75.4,E75.6,E76.01-E76.1,E76.210-E76.9,E77.0,E77.8,E78.70,E78.9,E80.0-E80.1,E80.20-E80.3,E88.40-E88.89,H49.811-H49.819
CPT: 93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99195,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **61**
Condition: TORSION OF OVARY (See Guideline Notes 64,65)
Treatment: OOPHORECTOMY, OVARIAN CYSTECTOMY
ICD-10: N83.511-N83.53
CPT: 58660-58662,58700-58740,58770,58925-58943,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **62**
Condition: SUBSTANCE-INDUCED MOOD, ANXIETY, DELUSIONAL AND OBSESSIVE-COMPULSIVE DISORDERS (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F10.14,F10.150-F10.180,F10.188,F10.24,F10.250-F10.259,F10.280,F10.288,F10.94,F10.950-F10.959,F10.980,F10.988,F11.14,F11.150-F11.159,F11.188,F11.24,F11.250-F11.259,F11.288,F11.94,F11.950-F11.959,F11.988,F12.150-F12.180,F12.250-F12.280,F12.950-F12.980,F13.14,F13.150-F13.180,F13.188,F13.24,F13.250-F13.259,F13.280,F13.288,F13.94,F13.950-F13.959,F13.980,F13.988,F14.14,F14.150-F14.180,F14.188,F14.24;F14.250-F14.280,F14.288,F14.94,F14.950-F14.980,F14.988,F15.14,F15.150-F15.180,F15.188,F15.24,F15.250-F15.280,F15.288,F15.94,F15.950-F15.980,F15.988,F16.14,F16.150-F16.188,F16.24,F16.250-F16.288,F16.94,F16.950-F16.988,F18.14,F18.150-F18.159,F18.180-F18.188,F18.24,F18.250-F18.259,F18.280-F18.288,F18.94,F18.950-F18.959,F18.980-F18.988,F19.14,F19.150-F19.159,F19.180,F19.188,F19.24,F19.250-F19.259,F19.280,F19.288,F19.94,F19.950-F19.959,F19.980,F19.988
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,97810-97814,98966-98969,99051,99060,99201-99239,99281-99285,99291,99292,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004-H0006,H0010,H0011,H0013-H0016,H0020,H0032-H0035,H0045,H2013,T1006,T1007

Line: **63**
Condition: SPONTANEOUS ABORTION; MISSED ABORTION (See Guideline Notes 64,65,99)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: O02.0-O02.1,O02.81-O02.9,O03.0-O03.2,O03.30-O03.86,O03.88-O03.9,O36.80X0-O36.80X9,Z31.82
CPT: 58150,58152,58520,59135,59136,59200,59812-59830,59855-59857,76801-76810,76815-76817,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S0199

Line: **64**
Condition: CONGENITAL ANOMALIES OF UPPER ALIMENTARY TRACT, EXCLUDING TONGUE (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: Q38.4-Q38.8,Q39.0-Q39.9,Q40.0-Q40.9,Q93.81
CPT: 31750,31760,42145,42200,42215,42815-42826,42950,43112-43124,43196,43226,43248,43249,43279,43283,43286-43288,43300-43331,43338-43361,43420,43450,43453,43496,43520,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **65**
Condition: SUBSTANCE-INDUCED DELIRIUM; SUBSTANCE INTOXICATION AND WITHDRAWAL
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F10.120-F10.129,F10.220-F10.239,F10.920-F10.929,F11.120-F11.129,F11.220-F11.23,F11.920-F11.93,F12.120-F12.129,F12.220-F12.229,F12.920-F12.929,F13.120-F13.129,F13.220-F13.239,F13.26-F13.27,F13.920-F13.939,F13.96-F13.97,F14.120-F14.129,F14.220-F14.23,F14.920-F14.929,F15.120-F15.129,F15.220-F15.23,F15.920-F15.93,F16.120-F16.129,F16.220-F16.229,F16.920-F16.929,F18.120-F18.129,F18.17,F18.220-F18.229,F18.27,F18.920-F18.929,F18.97,F19.120-F19.129,F19.16-F19.17,F19.220-F19.239,F19.26-F19.27,F19.920-F19.939,F19.96-F19.97
CPT: 90785,90832-90840,93792,93793,97810-97814,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,H0010,H0011,H0013-H0015,H0032,H0033,H0035,H0038,H2013

Line: **66**
Condition: LARYNGEAL STENOSIS OR PARALYSIS WITH AIRWAY COMPLICATIONS (See Guideline Notes 64,65,141)
Treatment: INCISION/EXCISION/ENDOSCOPY
ICD-10: J38.01-J38.02,J38.6
CPT: 31528,31529,31551-31554,31561-31571,31574,31590,31591,64905,92507,92508,92524,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **67**
Condition: VENTRICULAR SEPTAL DEFECT (See Guideline Notes 64,65)
Treatment: CLOSURE
ICD-10: Q21.0,Z79.01
CPT: 33610,33620,33621,33647,33665,33675-33688,33735-33737,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93355,93581,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **68**
Condition: ACUTE BACTERIAL MENINGITIS (See Guideline Notes 6,64,65)
Treatment: MEDICAL THERAPY
ICD-10: A02.21,A20.3,A32.11-A32.12,A39.0,A39.3,A39.81-A39.82,G00.0-G00.9,G01-G02,G04.2
CPT: 61000-61070,61107,61210,61215,92507,92508,92521-92526,92607-92609,92633,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9152

Line: **69**
Condition: ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION (See Guideline Notes 49,64,65,111)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: I20.0,I21.01-I21.A9,I22.0-I22.9,I23.1-I23.5,I23.7-I23.8,I24.0-I24.9,I25.110,I25.700,I25.710,I25.720,I25.730,I25.750,I25.760,I25.790,I51.81,R57.0,T81.11XA-T81.11XD,Z45.010-Z45.09
CPT: 33202,33206-33210,33212-33229,33233-33238,33310,33315,33361-33430,33465,33475,33477,33500,33508-33545,33572,33681,33922,33946-33974,33984-33989,35001,35182,35189,35226,35256,35286,35572,35600,92920-92944,92960-92998,93279-93284,93286-93289,93292-93296,93355,93724,93745,93792-93798,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,K0606-K0609,S0340-S0342,S2205-S2209

Line: **70**
Condition: CONGENITAL PULMONARY VALVE ANOMALIES (See Guideline Notes 64,65)
Treatment: PULMONARY VALVE REPAIR
ICD-10: Q22.1-Q22.3,Q24.3
CPT: 33470-33476,33478,33496,33530,33608,33620,33621,33768,33946-33966,33969,33984-33989,37246,37247,75557-75565,75573,92986-92990,93355,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 71

Condition: NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES (See Coding Specification Below) (See Guideline Notes 6,64,65,129,170)

Treatment: MEDICAL AND SURGICAL TREATMENT (E.G., G-TUBES, J-TUBES, RESPIRATORS, TRACHEOSTOMY, UROLOGICAL PROCEDURES)

ICD-10: A33,A50.40,A50.43,A50.45,A52.10-A52.15,A52.17-A52.19,A52.3,A81.00-A81.83,A87.1-A87.2,A88.8,A89,C70.0-C70.9,C71.0-C71.9,C72.0-C72.1,C72.20-C72.9,D33.9,D81.3,D81.5,E00.0-E00.9,E45,E70.20-E70.29,E70.330-E70.331,E70.8-E70.9,E71.0,E71.110-E71.548,E72.00-E72.51,E72.59-E72.9,E74.00-E74.09,E75.00-E75.09,E75.11-E75.23,E75.240-E75.6,E76.01-E76.1,E76.210-E76.9,E77.0-E77.9,E78.70-E78.9,E79.1-E79.9,E80.0-E80.1,E80.20-E80.3,E83.00-E83.09,E88.2,E88.40-E88.49,E88.89,F01.50-F01.51,F03.90-F03.91,F06.1,F06.8,F07.89,F71-F79,F84.0-F84.3,F84.8,G04.1,G04.81-G04.91,G10,G11.0-G11.4,G12.0-G12.1,G12.21-G12.9,G13.1-G13.8,G14-G20,G21.0,G21.11-G21.9,G23.0-G23.9,G25.82,G25.9,G30.0-G30.8,G31.01-G31.83,G31.85-G31.9,G32.0,G32.81-G32.89,G35,G36.0-G36.9,G37.0-G37.9,G40.011-G40.019,G40.111-G40.119,G40.211-G40.219,G40.311-G40.319,G40.411-G40.419,G40.811,G40.89,G40.911-G40.919,G60.0-G60.1,G60.3-G60.8,G61.0-G61.1,G61.81-G61.89,G62.0-G62.2,G62.81-G62.89,G64,G71.0,G71.11-G71.8,G72.0-G72.3,G72.41-G72.89,G73.7,G80.0-G80.9,G81.00-G81.94,G82.20-G82.54,G83.0,G83.30-G83.9,G90.01-G90.1,G90.3-G90.4,G91.0-G91.9,G92,G93.0-G93.1,G93.40-G93.81,G93.89,G94,G95.0,G95.11-G95.89,G97.0,G97.2,G97.31-G97.32,G97.48-G97.49,G97.61-G97.82,G98.0,G99.0-G99.8,H49.811-H49.819,I61.0-I61.9,I62.00-I62.9,I63.30,I63.311-I63.312,I63.319-I63.322,I63.329-I63.332,I63.339-I63.342,I63.349-I63.412,I63.419-I63.422,I63.429-I63.432,I63.439-I63.442,I63.449-I63.512,I63.519-I63.522,I63.529-I63.532,I63.539-I63.542,I63.549-I63.9,I67.3,I67.81-I67.83,I67.841-I67.89,I69.010-I69.018,I69.020-I69.022,I69.051-I69.069,I69.091-I69.092,I69.110-I69.118,I69.121-I69.122,I69.128,I69.151-I69.169,I69.191-I69.192,I69.210-I69.218,I69.221-I69.222,I69.251-I69.269,I69.291-I69.292,I69.310-I69.318,I69.321-I69.322,I69.351-I69.369,I69.391-I69.392,I69.810-I69.818,I69.822,I69.851-I69.869,I69.891-I69.892,I69.910-I69.918,I69.922,I69.951-I69.969,I69.991-I69.992,I97.810-I97.821,K59.2,M62.3,M62.58-M62.59,M62.89,N31.0-N31.9,P07.00-P07.39,P10.0-P10.9,P11.0,P11.2,P11.5-P11.9,P19.0-P19.9,P24.00-P24.21,P24.80-P24.9,P35.0-P35.9,P37.0-P37.9,P39.2,P50.0-P50.9,P51.0-P51.9,P52.0-P52.1,P52.21-P52.9,P54.1-P54.9,P55.1-P55.9,P56.0,P56.90-P56.99,P57.0,P91.2,P91.60-P91.63,P96.81,Q00.0-Q00.2,Q01.0-Q01.9,Q02,Q03.0-Q03.9,Q04.0-Q04.9,Q05.0-Q05.9,Q06.0-Q06.9,Q07.00-Q07.9,Q74.3,Q77.3,Q77.6,Q78.0-Q78.3,Q78.5-Q78.6,Q85.1,Q86.0-Q86.8,Q87.1-Q87.3,Q87.40,Q87.410-Q87.89,Q89.4-Q89.8,Q90.0-Q90.9,Q91.0-Q91.7,Q92.0-Q92.5,Q92.62-Q92.9,Q93.0-Q93.7,Q93.81-Q93.9,Q95.2-Q95.8,Q96.0-Q96.9,Q97.0-Q97.8,Q98.0-Q98.3,Q98.5-Q98.8,Q99.0-Q99.8,R13.0,R13.10-R13.19,R15.0,R15.2-R15.9,R41.4,R41.81,R53.2,R54,S06.370A-S06.370D,S06.810A-S06.810D,S06.811A-S06.811D,S06.812A-S06.812D,S06.813A-S06.813D,S06.814A-S06.814D,S06.815A-S06.815D,S06.816A-S06.816D,S06.817A-S06.819D,S06.820A-S06.820D,S06.821A-S06.821D,S06.822A-S06.822D,S06.823A-S06.823D,S06.824A-S06.824D,S06.825A-S06.825D,S06.826A-S06.826D,S06.827A-S06.829D,S06.890A-S06.890D,S06.891A-S06.891D,S06.892A-S06.892D,S06.893A-S06.893D,S06.894A-S06.894D,S06.895A-S06.895D,S06.896A-S06.896D,S06.897A-S06.899D,S06.9X0A-S06.9X0D,S06.9X1A-S06.9X1D,S06.9X2A-S06.9X2D,S06.9X3A-S06.9X3D,S06.9X4A-S06.9X4D,S06.9X5A-S06.9X5D,S06.9X6A-S06.9X6D,S06.9X7A-S06.9X9D,S14.0XXA-S14.0XXD,S14.101A-S14.101D,S14.102A-S14.102D,S14.103A-S14.103D,S14.104A-S14.104D,S14.105A-S14.105D,S14.106A-S14.106D,S14.107A-S14.107D,S14.108A-S14.108D,S14.109A-S14.109D,S14.111A-S14.111D,S14.112A-S14.112D,S14.113A-S14.113D,S14.114A-S14.114D,S14.115A-S14.115D,S14.116A-S14.116D,S14.117A-S14.117D,S14.118A-S14.118D,S14.119A-S14.119D,S14.121A-S14.121D,S14.122A-S14.122D,S14.123A-S14.123D,S14.124A-S14.124D,S14.125A-S14.125D,S14.126A-S14.126D,S14.127A-S14.127D,S14.128A-S14.128D,S14.129A-S14.129D,S14.131A-S14.131D,S14.132A-S14.132D,S14.133A-S14.133D,S14.134A-S14.134D,S14.135A-S14.135D,S14.136A-S14.136D,S14.137A-S14.137D,S14.138A-S14.138D,S14.139A-S14.139D,S14.141A-S14.141D,S14.142A-S14.142D,S14.143A-S14.143D,S14.144A-S14.144D,S14.145A-S14.145D,S14.146A-S14.146D,S14.147A-S14.147D,S14.148A-S14.148D,S14.149A-S14.149D,S14.151A-S14.151D,S14.152A-S14.152D,S14.153A-S14.153D,S14.154A-S14.154D,S14.155A-S14.155D,S14.156A-S14.156D,S14.157A-S14.157D,S14.158A-S14.158D,S14.159A-S14.159D,S14.2XXA-S14.2XXD,S14.3XXA-S14.3XXD,S24.0XXA-S24.0XXD,S24.101A-S24.101D,S24.102A-S24.102D,S24.103A-S24.103D,S24.104A-S24.104D,S24.109A-S24.109D,S24.111A-S24.111D,S24.112A-S24.112D,S24.113A-S24.113D,S24.114A-S24.114D,S24.119A-S24.119D,S24.131A-S24.131D,S24.132A-S24.132D,S24.133A-S24.133D,S24.134A-S24.134D,S24.139A-S24.139D,S24.141A-S24.141D,S24.142A-S24.142D,S24.143A-S24.143D,S24.144A-S24.144D,S24.149A-S24.149D,S24.151A-S24.151D,S24.152A-S24.152D,S24.153A-S24.153D,S24.154A-S24.154D,S24.159A-S24.159D,S24.2XXA-S24.2XXD,S34.01XA-S34.01XD,S34.02XA-S34.02XD,S34.101A-S34.101D,S34.102A-S34.102D,S34.103A-S34.103D,S34.104A-S34.104D,S34.105A-S34.105D,S34.109A-S34.109D,S34.111A-S34.111D,S34.112A-S34.112D,S34.113A-S34.113D,S34.114A-S34.114D,S34.115A-S34.115D,S34.119A-S34.119D,S34.121A-S34.121D,S34.122A-S34.122D,S34.123A-S34.123D,S34.124A-S34.124D,S34.125A-S34.125D,S34.129A-S34.129D,S34.131A-S34.131D,S34.132A-S34.132D,S34.139A-S34.139D,S34.21XA-S34.21XD,S34.22XA-S34.22XD,S34.3XXA-S34.3XXD,S34.4XXA-S34.4XXD,T40.0X1A-T40.0X1D,T40.0X2A-T40.0X2D,T40.0X3A-T40.0X3D,T40.0X4A-T40.0X4D,T40.1X1A-T40.1X1D,T40.1X2A-T40.1X2D,T40.1X3A-T40.1X3D,T40.1X4A-T40.1X4D,T40.2X1A-T40.2X1D,T40.2X2A-T40.2X2D,T40.2X3A-T40.2X3D,T40.2X4A-T40.2X4D,T40.3X1A-T40.3X1D,T40.3X2A-T40.3X2D,T40.3X3A-T40.3X3D,T40.3X4A-T40.3X4D,T40.4X1A-T40.4X1D,T40.4X2A-T40.4X2D,T40.4X3A-T40.4X3D,T40.4X4A-T40.4X4D,T40.5X1A-T40.5X1D,T40.5X2A-T40.5X2D,T40.5X3A-T40.5X3D,T40.5X4A-T40.5X4D,T40.601A-T40.601D,T40.602A-T40.602D,T40.603A-T40.603D,T40.604A-T40.604D,T40.691A-T40.691D,T40.692A-T40.692D,T40.693A-T40.693D,T40.694A-T40.694D,T40.7X1A-T40.7X1D,T40.7X2A-T40.7X2D,T40.7X3A-T40.7X3D,T40.7X4A-T40.7X4D,T40.8X1A-T40.8X1D,T40.8X2A-T40.8X2D,T40.8X3A-T40.8X3D,T40.8X4A-T40.8X4D,T40.901A-T40.901D,T40.902A-T40.902D,T40.903A-T40.903D,T40.904A-T40.904D,T40.991A-T40.991D,T71.111A-T71.111D,T71.112A-T71.112D,T71.113A-T71.113D,T71.114A-T71.114D,T71.121A-T71.121D,T71.122A-T71.122D,T71.123A-T71.123D,T71.124A-T71.124D,T71.131A-T71.131D,T71.132A-T71.132D,T71.133A-T71.133D,T71.134A-T71.134D,T71.141A-

T71.141D,T71.143A-T71.143D,T71.144A-T71.144D,T71.151A-T71.151D,T71.152A-T71.152D,T71.153A-T71.153D,T71.154A-T71.154D,T71.161A-T71.161D,T71.162A-T71.162D,T71.163A-T71.163D,T71.164A-T71.164D,T71.191A-T71.191D,T71.192A-T71.192D,T71.193A-T71.193D,T71.194A-T71.194D,T71.20XA-T71.20XD,T71.21XA-T71.21XD,T71.221A-T71.221D,T71.222A-T71.222D,T71.223A-T71.223D,T71.224A-T71.224D,T71.231A-T71.231D,T71.232A-T71.232D,T71.233A-T71.233D,T71.234A-T71.234D,T71.29XA-T71.29XD,T71.9XXA-T71.9XXD,T74.4XXA-T74.4XXD,T75.01XA-T75.01XD,T75.09XA-T75.09XD,T75.1XXA-T75.1XXD,T75.4XXA-T75.4XXD,T78.00XA-T78.00XD,T78.01XA-T78.01XD,T78.02XA-T78.02XD,T78.03XA-T78.03XD,T78.04XA-T78.04XD,T78.05XA-T78.05XD,T78.06XA-T78.06XD,T78.07XA-T78.07XD,T78.08XA-T78.08XD,T78.09XA-T78.09XD,T78.3XXA-T78.3XXD,T78.8XXA-T78.8XXD,T79.0XXA-T79.0XXD,T79.4XXA-T79.4XXD,T79.6XXA-T79.6XXD,T88.2XXA-T88.2XXD,T88.51XA-T88.51XD,T88.6XXA-T88.6XXD,Z43.0-Z43.4,Z43.8,Z45.49,Z46.59

CPT: 15845,31600,31601,31610-31614,31630,31631,31636-31638,31641,31730-31760,31820-31830,43810-43825,44130,44139-44160,44186-44188,44204-44213,44300-44320,44620-44626,44701,46750-46754,49442,51040,51102,51700,51705,51710,51880,51960,52277,53431-53442,53445,61215,62320-62323,62350-62362,62367-62370,77387,77401-77432,77469,77470,92526,93792,93793,94002-94005,94640,94660-94668,95990,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: D5937,D5992,D5993,G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

CPT codes 62320-3 are only included on Lines 71 and 292 for trials of antispasmodics in preparation for placement of a baclofen pump.

Line: 72
Condition: BURN, PARTIAL THICKNESS GREATER THAN 30% OF BODY SURFACE OR WITH VITAL SITE; FULL THICKNESS, LESS THAN 10% OF BODY SURFACE (See Guideline Notes 6,64,65)
Treatment: FREE SKIN GRAFT, MEDICAL THERAPY
ICD-10: L00,L49.7,T20.20XA-T20.20XD,T20.211A-T20.211D,T20.212A-T20.212D,T20.219A-T20.219D,T20.22XA-T20.22XD,T20.23XA-T20.23XD,T20.24XA-T20.24XD,T20.25XA-T20.25XD,T20.26XA-T20.26XD,T20.27XA-T20.27XD,T20.29XA-T20.29XD,T20.30XA-T20.30XD,T20.311A-T20.311D,T20.312A-T20.312D,T20.319A-T20.319D,T20.32XA-T20.32XD,T20.33XA-T20.33XD,T20.34XA-T20.34XD,T20.37XA-T20.37XD,T20.39XA-T20.39XD,T20.60XA-T20.60XD,T20.611A-T20.611D,T20.612A-T20.612D,T20.619A-T20.619D,T20.62XA-T20.62XD,T20.63XA-T20.63XD,T20.64XA-T20.64XD,T20.65XA-T20.65XD,T20.66XA-T20.66XD,T20.67XA-T20.67XD,T20.69XA-T20.69XD,T20.70XA-T20.70XD,T20.711A-T20.711D,T20.712A-T20.712D,T20.719A-T20.719D,T20.72XA-T20.72XD,T20.73XA-T20.73XD,T20.74XA-T20.74XD,T20.77XA-T20.77XD,T20.79XA-T20.79XD,T21.20XA-T21.20XD,T21.21XA-T21.21XD,T21.22XA-T21.22XD,T21.23XA-T21.23XD,T21.24XA-T21.24XD,T21.25XA-T21.25XD,T21.26XA-T21.26XD,T21.27XA-T21.27XD,T21.29XA-T21.29XD,T21.36XA-T21.36XD,T21.37XA-T21.37XD,T21.60XA-T21.60XD,T21.61XA-T21.61XD,T21.62XA-T21.62XD,T21.63XA-T21.63XD,T21.64XA-T21.64XD,T21.65XA-T21.65XD,T21.66XA-T21.66XD,T21.67XA-T21.67XD,T21.69XA-T21.69XD,T21.76XA-T21.76XD,T21.77XA-T21.77XD,T22.20XA-T22.20XD,T22.211A-T22.211D,T22.212A-T22.212D,T22.219A-T22.219D,T22.221A-T22.221D,T22.222A-T22.222D,T22.229A-T22.229D,T22.231A-T22.231D,T22.232A-T22.232D,T22.239A-T22.239D,T22.241A-T22.241D,T22.242A-T22.242D,T22.249A-T22.249D,T22.251A-T22.251D,T22.252A-T22.252D,T22.259A-T22.259D,T22.261A-T22.261D,T22.262A-T22.262D,T22.269A-T22.269D,T22.291A-T22.291D,T22.292A-T22.292D,T22.299A-T22.299D,T22.60XA-T22.60XD,T22.611A-T22.611D,T22.612A-T22.612D,T22.619A-T22.619D,T22.621A-T22.621D,T22.622A-T22.622D,T22.629A-T22.629D,T22.631A-T22.631D,T22.632A-T22.632D,T22.639A-T22.639D,T22.641A-T22.641D,T22.642A-T22.642D,T22.649A-T22.649D,T22.651A-T22.651D,T22.652A-T22.652D,T22.659A-T22.659D,T22.661A-T22.661D,T22.662A-T22.662D,T22.669A-T22.669D,T22.691A-T22.691D,T22.692A-T22.692D,T22.699A-T22.699D,T23.201A-T23.201D,T23.202A-T23.202D,T23.209A-T23.209D,T23.211A-T23.211D,T23.212A-T23.212D,T23.219A-T23.219D,T23.221A-T23.221D,T23.222A-T23.222D,T23.229A-T23.229D,T23.231A-T23.231D,T23.232A-T23.232D,T23.239A-T23.239D,T23.241A-T23.241D,T23.242A-T23.242D,T23.249A-T23.249D,T23.251A-T23.251D,T23.252A-T23.252D,T23.259A-T23.259D,T23.261A-T23.261D,T23.262A-T23.262D,T23.269A-T23.269D,T23.271A-T23.271D,T23.272A-T23.272D,T23.279A-T23.279D,T23.291A-T23.291D,T23.292A-T23.292D,T23.299A-T23.299D,T23.351A-T23.351D,T23.352A-T23.352D,T23.359A-T23.359D,T23.601A-T23.601D,T23.602A-T23.602D,T23.609A-T23.609D,T23.611A-T23.611D,T23.612A-T23.612D,T23.619A-T23.619D,T23.621A-T23.621D,T23.622A-T23.622D,T23.629A-T23.629D,T23.631A-T23.631D,T23.632A-T23.632D,T23.639A-T23.639D,T23.641A-T23.641D,T23.642A-T23.642D,T23.649A-T23.649D,T23.651A-T23.651D,T23.652A-T23.652D,T23.659A-T23.659D,T23.661A-T23.661D,T23.662A-T23.662D,T23.669A-T23.669D,T23.671A-T23.671D,T23.672A-T23.672D,T23.679A-T23.679D,T23.691A-T23.691D,T23.692A-T23.692D,T23.699A-T23.699D,T23.751A-T23.751D,T23.752A-T23.752D,T23.759A-T23.759D,T24.201A-T24.201D,T24.202A-T24.202D,T24.209A-T24.209D,T24.211A-T24.211D,T24.212A-T24.212D,T24.219A-T24.219D,T24.221A-T24.221D,T24.222A-T24.222D,T24.229A-T24.229D,T24.231A-T24.231D,T24.232A-T24.232D,T24.239A-T24.239D,T24.291A-T24.291D,T24.292A-T24.292D,T24.299A-T24.299D,T24.601A-T24.601D,T24.602A-T24.602D,T24.609A-T24.609D,T24.611A-T24.611D,T24.612A-T24.612D,T24.619A-T24.619D,T24.621A-T24.621D,T24.622A-T24.622D,T24.629A-T24.629D,T24.631A-T24.631D,T24.632A-T24.632D,T24.639A-T24.639D,T24.691A-T24.691D,T24.692A-T24.692D,T24.699A-T24.699D,T25.211A-T25.211D,T25.212A-T25.212D,T25.219A-T25.219D,T25.221A-T25.221D,T25.222A-T25.222D,T25.229A-T25.229D,T25.231A-T25.231D,T25.232A-T25.232D,T25.239A-T25.239D,T25.291A-T25.291D,T25.292A-T25.292D,T25.299A-T25.299D,T25.321A-T25.321D,T25.322A-T25.322D,T25.329A-T25.329D,T25.611A-T25.611D,T25.612A-T25.612D,T25.619A-T25.619D,T25.621A-T25.621D,T25.622A-T25.622D,T25.629A-T25.629D,T25.631A-T25.631D,T25.632A-T25.632D,T25.639A-T25.639D,T25.691A-T25.691D,T25.692A-T25.692D,T25.699A-T25.699D,T25.721A-T25.721D,T25.722A-

T25.722D,T25.729A-T25.729D,T31.0,T31.10,T31.20,T31.30,T31.40,T31.50,T31.60,T31.70,T31.80,T31.90,T32.0, T32.10,T32.20,T32.30,T32.40,T32.50,T32.60,T32.70,T32.80,T32.90
CPT: 11000,11042,11045,11960-11971,15002-15005,15271-15278,16020-16036,92507,92508,92521-92524,92607-92609,92633,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763, 98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513,G0514,S9152

Line: **73**
Condition: POLYCYTHEMIA NEONATORUM, SYMPTOMATIC (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: P61.1
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **74**
Condition: DERMATOMYOSITIS, POLYMYOSITIS (See Guideline Notes 6,64,65)
Treatment: MEDICAL THERAPY
ICD-10: M33.00-M33.99,M35.8,M36.0
CPT: 90284,93792,93793,96150-96155,97110,97116,97161-97168,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **75**
Condition: ADDISON'S DISEASE (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: E27.1-E27.3,E27.40-E27.49,E31.0,E31.8-E31.9,E89.6
CPT: 92081-92083,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **76**
Condition: HYPERTENSION AND HYPERTENSIVE DISEASE (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: I10,I11.0-I11.9,I15.2-I15.9,I16.0-I16.9,I67.4
CPT: 92960-92971,92978-92998,93792-93798,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078, 99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line: **77**
Condition: PATENT DUCTUS ARTERIOSUS; AORTIC PULMONARY FISTULA/WINDOW (See Guideline Notes 64,65)
Treatment: LIGATION
ICD-10: P29.30-P29.38,Q21.4,Q25.0
CPT: 33500-33504,33702,33710,33813-33824,33946-33966,33969,33984-33989,92960-92971,92978-92998,93355, 93582,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285, 99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line: **78**
Condition: INJURY TO MAJOR BLOOD VESSELS
Treatment: LIGATION/REPAIR
ICD-10: S09.0XXA-S09.0XXD,S15.001A-S15.001D,S15.002A-S15.002D,S15.009A-S15.009D,S15.011A-S15.011D, S15.012A-S15.012D,S15.019A-S15.019D,S15.021A-S15.021D,S15.022A-S15.022D,S15.029A-S15.029D, S15.091A-S15.091D,S15.092A-S15.092D,S15.099A-S15.099D,S15.101A-S15.101D,S15.102A-S15.102D, S15.109A-S15.109D,S15.111A-S15.111D,S15.112A-S15.112D,S15.119A-S15.119D,S15.121A-S15.121D, S15.122A-S15.122D,S15.129A-S15.129D,S15.191A-S15.191D,S15.192A-S15.192D,S15.199A-S15.199D, S15.201A-S15.201D,S15.202A-S15.202D,S15.209A-S15.209D,S15.211A-S15.211D,S15.212A-S15.212D, S15.219A-S15.219D,S15.221A-S15.221D,S15.222A-S15.222D,S15.229A-S15.229D,S15.291A-S15.291D, S15.292A-S15.292D,S15.299A-S15.299D,S15.301A-S15.301D,S15.302A-S15.302D,S15.309A-S15.309D, S15.311A-S15.311D,S15.312A-S15.312D,S15.319A-S15.319D,S15.321A-S15.321D,S15.322A-S15.322D, S15.329A-S15.329D,S15.391A-S15.391D,S15.392A-S15.392D,S15.399A-S15.399D,S15.8XXA-S15.8XXD, S15.9XXA-S15.9XXD,S25.00XA-S25.00XD,S25.01XA-S25.01XD,S25.02XA-S25.02XD,S25.09XA-S25.09XD, S25.101A-S25.101D,S25.102A-S25.102D,S25.109A-S25.109D,S25.111A-S25.111D,S25.112A-S25.112D,

S25.119A-S25.119D,S25.121A-S25.121D,S25.122A-S25.122D,S25.129A-S25.129D,S25.191A-S25.191D,
S25.192A-S25.192D,S25.199A-S25.199D,S25.20XA-S25.20XD,S25.21XA-S25.21XD,S25.22XA-S25.22XD,
S25.29XA-S25.29XD,S25.301A-S25.301D,S25.302A-S25.302D,S25.309A-S25.309D,S25.311A-S25.311D,
S25.312A-S25.312D,S25.319A-S25.319D,S25.321A-S25.321D,S25.322A-S25.322D,S25.329A-S25.329D,
S25.391A-S25.391D,S25.392A-S25.392D,S25.399A-S25.399D,S25.401A-S25.401D,S25.402A-S25.402D,
S25.409A-S25.409D,S25.411A-S25.411D,S25.412A-S25.412D,S25.419A-S25.419D,S25.421A-S25.421D,
S25.422A-S25.422D,S25.429A-S25.429D,S25.491A-S25.491D,S25.492A-S25.492D,S25.499A-S25.499D,
S25.501A-S25.501D,S25.502A-S25.502D,S25.509A-S25.509D,S25.511A-S25.511D,S25.512A-S25.512D,
S25.519A-S25.519D,S25.591A-S25.591D,S25.592A-S25.592D,S25.599A-S25.599D,S25.801A-S25.801D,
S25.802A-S25.802D,S25.809A-S25.809D,S25.811A-S25.811D,S25.812A-S25.812D,S25.819A-S25.819D,
S25.891A-S25.891D,S25.892A-S25.892D,S25.899A-S25.899D,S25.90XA-S25.90XD,S25.91XA-S25.91XD,
S25.99XA-S25.99XD,S35.00XA-S35.00XD,S35.01XA-S35.01XD,S35.02XA-S35.02XD,S35.09XA-S35.09XD,
S35.10XA-S35.10XD,S35.11XA-S35.11XD,S35.12XA-S35.12XD,S35.19XA-S35.19XD,S35.211A-S35.211D,
S35.212A-S35.212D,S35.218A-S35.218D,S35.219A-S35.219D,S35.221A-S35.221D,S35.222A-S35.222D,
S35.228A-S35.228D,S35.229A-S35.229D,S35.231A-S35.231D,S35.232A-S35.232D,S35.238A-S35.238D,
S35.239A-S35.239D,S35.291A-S35.291D,S35.292A-S35.292D,S35.298A-S35.298D,S35.299A-S35.299D,
S35.311A-S35.311D,S35.318A-S35.318D,S35.319A-S35.319D,S35.321A-S35.321D,S35.328A-S35.328D,
S35.329A-S35.329D,S35.331A-S35.331D,S35.338A-S35.338D,S35.339A-S35.339D,S35.341A-S35.341D,
S35.348A-S35.348D,S35.349A-S35.349D,S35.401A-S35.401D,S35.402A-S35.402D,S35.403A-S35.403D,
S35.404A-S35.404D,S35.405A-S35.405D,S35.406A-S35.406D,S35.411A-S35.411D,S35.412A-S35.412D,
S35.413A-S35.413D,S35.414A-S35.414D,S35.415A-S35.415D,S35.416A-S35.416D,S35.491A-S35.491D,
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S35.50XA-S35.50XD,S35.511A-S35.511D,S35.512A-S35.512D,S35.513A-S35.513D,S35.514A-S35.514D,
S35.515A-S35.515D,S35.516A-S35.516D,S35.531A-S35.531D,S35.532A-S35.532D,S35.533A-S35.533D,
S35.534A-S35.534D,S35.535A-S35.535D,S35.536A-S35.536D,S35.59XA-S35.59XD,S45.001A-S45.001D,
S45.002A-S45.002D,S45.009A-S45.009D,S45.011A-S45.011D,S45.012A-S45.012D,S45.019A-S45.019D,
S45.091A-S45.091D,S45.092A-S45.092D,S45.099A-S45.099D,S45.101A-S45.101D,S45.102A-S45.102D,
S45.109A-S45.109D,S45.111A-S45.111D,S45.112A-S45.112D,S45.119A-S45.119D,S45.191A-S45.191D,
S45.192A-S45.192D,S45.199A-S45.199D,S45.201A-S45.201D,S45.202A-S45.202D,S45.209A-S45.209D,
S45.211A-S45.211D,S45.212A-S45.212D,S45.219A-S45.219D,S45.291A-S45.291D,S45.292A-S45.292D,
S45.299A-S45.299D,S45.801A-S45.801D,S45.802A-S45.802D,S45.809A-S45.809D,S45.811A-S45.811D,
S45.812A-S45.812D,S45.819A-S45.819D,S45.891A-S45.891D,S45.892A-S45.892D,S45.899A-S45.899D,
S45.901A-S45.901D,S45.902A-S45.902D,S45.909A-S45.909D,S45.911A-S45.911D,S45.912A-S45.912D,
S45.919A-S45.919D,S45.991A-S45.991D,S45.992A-S45.992D,S45.999A-S45.999D,S55.001A-S55.001D,
S55.002A-S55.002D,S55.009A-S55.009D,S55.011A-S55.011D,S55.012A-S55.012D,S55.019A-S55.019D,
S55.091A-S55.091D,S55.092A-S55.092D,S55.099A-S55.099D,S55.101A-S55.101D,S55.102A-S55.102D,
S55.109A-S55.109D,S55.111A-S55.111D,S55.112A-S55.112D,S55.119A-S55.119D,S55.191A-S55.191D,
S55.192A-S55.192D,S55.199A-S55.199D,S55.201A-S55.201D,S55.202A-S55.202D,S55.209A-S55.209D,
S55.211A-S55.211D,S55.212A-S55.212D,S55.219A-S55.219D,S55.291A-S55.291D,S55.292A-S55.292D,
S55.299A-S55.299D,S55.801A-S55.801D,S55.802A-S55.802D,S55.809A-S55.809D,S55.811A-S55.811D,
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S65.002A-S65.002D,S65.009A-S65.009D,S65.011A-S65.011D,S65.012A-S65.012D,S65.019A-S65.019D,
S65.091A-S65.091D,S65.092A-S65.092D,S65.099A-S65.099D,S65.101A-S65.101D,S65.102A-S65.102D,
S65.109A-S65.109D,S65.111A-S65.111D,S65.112A-S65.112D,S65.119A-S65.119D,S65.191A-S65.191D,
S65.192A-S65.192D,S65.199A-S65.199D,S65.201A-S65.201D,S65.202A-S65.202D,S65.209A-S65.209D,
S65.211A-S65.211D,S65.212A-S65.212D,S65.219A-S65.219D,S65.291A-S65.291D,S65.292A-S65.292D,
S65.299A-S65.299D,S65.301A-S65.301D,S65.302A-S65.302D,S65.309A-S65.309D,S65.311A-S65.311D,
S65.312A-S65.312D,S65.319A-S65.319D,S65.391A-S65.391D,S65.392A-S65.392D,S65.399A-S65.399D,
S65.801A-S65.801D,S65.802A-S65.802D,S65.809A-S65.809D,S65.811A-S65.811D,S65.812A-S65.812D,
S65.819A-S65.819D,S65.891A-S65.891D,S65.892A-S65.892D,S65.899A-S65.899D,S65.901A-S65.901D,
S65.902A-S65.902D,S65.909A-S65.909D,S65.911A-S65.911D,S65.912A-S65.912D,S65.919A-S65.919D,
S65.991A-S65.991D,S65.992A-S65.992D,S65.999A-S65.999D,S75.001A-S75.001D,S75.002A-S75.002D,
S75.009A-S75.009D,S75.011A-S75.011D,S75.012A-S75.012D,S75.019A-S75.019D,S75.021A-S75.021D,
S75.022A-S75.022D,S75.029A-S75.029D,S75.091A-S75.091D,S75.092A-S75.092D,S75.099A-S75.099D,
S75.101A-S75.101D,S75.102A-S75.102D,S75.109A-S75.109D,S75.111A-S75.111D,S75.112A-S75.112D,
S75.119A-S75.119D,S75.121A-S75.121D,S75.122A-S75.122D,S75.129A-S75.129D,S75.191A-S75.191D,
S75.192A-S75.192D,S75.199A-S75.199D,S75.201A-S75.201D,S75.202A-S75.202D,S75.209A-S75.209D,
S75.211A-S75.211D,S75.212A-S75.212D,S75.219A-S75.219D,S75.221A-S75.221D,S75.222A-S75.222D,
S75.229A-S75.229D,S75.291A-S75.291D,S75.292A-S75.292D,S75.299A-S75.299D,S75.801A-S75.801D,
S75.802A-S75.802D,S75.809A-S75.809D,S75.811A-S75.811D,S75.812A-S75.812D,S75.819A-S75.819D,
S75.891A-S75.891D,S75.892A-S75.892D,S75.899A-S75.899D,S75.901A-S75.901D,S75.902A-S75.902D,
S75.909A-S75.909D,S75.911A-S75.911D,S75.912A-S75.912D,S75.919A-S75.919D,S75.991A-S75.991D,
S75.992A-S75.992D,S75.999A-S75.999D,S85.001A-S85.001D,S85.002A-S85.002D,S85.009A-S85.009D,
S85.011A-S85.011D,S85.012A-S85.012D,S85.019A-S85.019D,S85.091A-S85.091D,S85.092A-S85.092D,
S85.099A-S85.099D,S85.101A-S85.101D,S85.102A-S85.102D,S85.109A-S85.109D,S85.111A-S85.111D,
S85.112A-S85.112D,S85.119A-S85.119D,S85.121A-S85.121D,S85.122A-S85.122D,S85.129A-S85.129D,
S85.131A-S85.131D,S85.132A-S85.132D,S85.139A-S85.139D,S85.141A-S85.141D,S85.142A-S85.142D,
S85.149A-S85.149D,S85.151A-S85.151D,S85.152A-S85.152D,S85.159A-S85.159D,S85.161A-S85.161D,
S85.162A-S85.162D,S85.169A-S85.169D,S85.171A-S85.171D,S85.172A-S85.172D,S85.179A-S85.179D,
S85.181A-S85.181D,S85.182A-S85.182D,S85.189A-S85.189D,S85.201A-S85.201D,S85.202A-S85.202D,

S85.209A-S85.209D,S85.211A-S85.211D,S85.212A-S85.212D,S85.219A-S85.219D,S85.291A-S85.291D, S85.292A-S85.292D,S85.299A-S85.299D,S85.301A-S85.301D,S85.302A-S85.302D,S85.309A-S85.309D, S85.311A-S85.311D,S85.312A-S85.312D,S85.319A-S85.319D,S85.391A-S85.391D,S85.392A-S85.392D, S85.399A-S85.399D,S85.401A-S85.401D,S85.402A-S85.402D,S85.409A-S85.409D,S85.411A-S85.411D, S85.412A-S85.412D,S85.419A-S85.419D,S85.491A-S85.491D,S85.492A-S85.492D,S85.499A-S85.499D, S85.501A-S85.501D,S85.502A-S85.502D,S85.509A-S85.509D,S85.511A-S85.511D,S85.512A-S85.512D, S85.519A-S85.519D,S85.591A-S85.591D,S85.592A-S85.592D,S85.599A-S85.599D,S85.801A-S85.801D, S85.802A-S85.802D,S85.809A-S85.809D,S85.811A-S85.811D,S85.812A-S85.812D,S85.819A-S85.819D, S85.891A-S85.891D,S85.892A-S85.892D,S85.899A-S85.899D,S85.901A-S85.901D,S85.902A-S85.902D, S85.909A-S85.909D,S85.911A-S85.911D,S85.912A-S85.912D,S85.919A-S85.919D,S85.991A-S85.991D, S85.992A-S85.992D,S85.999A-S85.999D

CPT: 32654,33320-33335,33880-33891,34502,34839-34848,35189-35206,35211,35216,35226-35246,35256-35276, 35286,35500,35506,35516,35616,37565,37615,37616,37618,37650,92960-92971,92986-92998,93792-93798, 98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line: 79
Condition: PHLEBITIS AND THROMBOPHLEBITIS, DEEP (See Guideline Notes 64,65,147)
Treatment: MEDICAL THERAPY
ICD-10: I80.10-I80.13,I80.201-I80.299,I82.401-I82.5Z9,Z79.01
CPT: 11042,11045,32661,35700,35860,35875,35876,35903,37187-37193,37212-37214,37248,37249,37500,37650, 37660,37735-37761,37785,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 80
Condition: INJURY TO INTERNAL ORGANS (See Guideline Notes 62,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: B51.0,S21.301A-S21.301D,S21.302A-S21.302D,S21.309A-S21.309D,S21.311A-S21.311D,S21.312A-S21.312D, S21.319A-S21.319D,S21.321A-S21.321D,S21.322A-S21.322D,S21.329A-S21.329D,S21.331A-S21.331D, S21.332A-S21.332D,S21.339A-S21.339D,S21.341A-S21.341D,S21.342A-S21.342D,S21.349A-S21.349D, S21.351A-S21.351D,S21.352A-S21.352D,S21.359A-S21.359D,S21.401A-S21.401D,S21.402A-S21.402D, S21.409A-S21.409D,S21.411A-S21.411D,S21.412A-S21.412D,S21.419A-S21.419D,S21.421A-S21.421D, S21.422A-S21.422D,S21.429A-S21.429D,S21.431A-S21.431D,S21.432A-S21.432D,S21.439A-S21.439D, S21.441A-S21.441D,S21.442A-S21.442D,S21.449A-S21.449D,S21.451A-S21.451D,S21.452A-S21.452D, S21.459A-S21.459D,S26.00XA-S26.00XD,S26.01XA-S26.01XD,S26.020A-S26.020D,S26.021A-S26.021D, S26.022A-S26.022D,S26.09XA-S26.09XD,S26.10XA-S26.10XD,S26.11XA-S26.11XD,S26.12XA-S26.12XD, S26.19XA-S26.19XD,S26.90XA-S26.90XD,S26.91XA-S26.91XD,S26.92XA-S26.92XD,S26.99XA-S26.99XD, S27.301A-S27.301D,S27.302A-S27.302D,S27.309A-S27.309D,S27.311A-S27.311D,S27.312A-S27.312D, S27.319A-S27.319D,S27.321A-S27.321D,S27.322A-S27.322D,S27.329A-S27.329D,S27.331A-S27.331D, S27.332A-S27.332D,S27.339A-S27.339D,S27.391A-S27.391D,S27.392A-S27.392D,S27.399A-S27.399D, S27.401A-S27.401D,S27.402A-S27.402D,S27.409A-S27.409D,S27.411A-S27.411D,S27.412A-S27.412D, S27.419A-S27.419D,S27.421A-S27.421D,S27.422A-S27.422D,S27.429A-S27.429D,S27.431A-S27.431D, S27.432A-S27.432D,S27.439A-S27.439D,S27.491A-S27.491D,S27.492A-S27.492D,S27.499A-S27.499D, S27.50XA-S27.50XD,S27.51XA-S27.51XD,S27.52XA-S27.52XD,S27.53XA-S27.53XD,S27.59XA-S27.59XD, S27.60XA-S27.60XD,S27.63XA-S27.63XD,S27.69XA-S27.69XD,S27.802A-S27.802D,S27.803A-S27.803D, S27.808A-S27.808D,S27.809A-S27.809D,S27.892A-S27.892D,S27.893A-S27.893D,S27.898A-S27.898D, S27.899A-S27.899D,S27.9XXA-S27.9XXD,S31.001A-S31.001D,S31.011A-S31.011D,S31.021A-S31.021D, S31.031A-S31.031D,S31.041A-S31.041D,S31.051A-S31.051D,S31.600A-S31.600D,S31.601A-S31.601D, S31.602A-S31.602D,S31.603A-S31.603D,S31.604A-S31.604D,S31.605A-S31.605D,S31.609A-S31.609D, S31.610A-S31.610D,S31.611A-S31.611D,S31.612A-S31.612D,S31.613A-S31.613D,S31.614A-S31.614D, S31.615A-S31.615D,S31.619A-S31.619D,S31.620A-S31.620D,S31.621A-S31.621D,S31.622A-S31.622D, S31.623A-S31.623D,S31.624A-S31.624D,S31.625A-S31.625D,S31.629A-S31.629D,S31.630A-S31.630D, S31.631A-S31.631D,S31.632A-S31.632D,S31.633A-S31.633D,S31.634A-S31.634D,S31.635A-S31.635D, S31.639A-S31.639D,S31.640A-S31.640D,S31.641A-S31.641D,S31.642A-S31.642D,S31.643A-S31.643D, S31.644A-S31.644D,S31.645A-S31.645D,S31.649A-S31.649D,S31.650A-S31.650D,S31.651A-S31.651D, S31.652A-S31.652D,S31.653A-S31.653D,S31.654A-S31.654D,S31.655A-S31.655D,S31.659A-S31.659D, S36.00XA-S36.00XD,S36.020A-S36.020D,S36.021A-S36.021D,S36.029A-S36.029D,S36.030A-S36.030D, S36.031A-S36.031D,S36.032A-S36.032D,S36.039A-S36.039D,S36.09XA-S36.09XD,S36.112A-S36.112D, S36.113A-S36.113D,S36.114A-S36.114D,S36.115A-S36.115D,S36.116A-S36.116D,S36.118A-S36.118D, S36.119A-S36.119D,S36.122A-S36.122D,S36.123A-S36.123D,S36.128A-S36.128D,S36.129A-S36.129D, S36.13XA-S36.13XD,S36.200A-S36.200D,S36.201A-S36.201D,S36.202A-S36.202D,S36.209A-S36.209D, S36.220A-S36.220D,S36.221A-S36.221D,S36.222A-S36.222D,S36.229A-S36.229D,S36.230A-S36.230D, S36.231A-S36.231D,S36.232A-S36.232D,S36.239A-S36.239D,S36.240A-S36.240D,S36.241A-S36.241D, S36.242A-S36.242D,S36.249A-S36.249D,S36.250A-S36.250D,S36.251A-S36.251D,S36.252A-S36.252D, S36.259A-S36.259D,S36.260A-S36.260D,S36.261A-S36.261D,S36.262A-S36.262D,S36.269A-S36.269D, S36.290A-S36.290D,S36.291A-S36.291D,S36.292A-S36.292D,S36.299A-S36.299D,S36.30XA-S36.30XD, S36.32XA-S36.32XD,S36.33XA-S36.33XD,S36.39XA-S36.39XD,S36.400A-S36.400D,S36.408A-S36.408D, S36.409A-S36.409D,S36.410A-S36.410D,S36.418A-S36.418D,S36.419A-S36.419D,S36.420A-S36.420D,

S36.428A-S36.428D,S36.429A-S36.429D,S36.430A-S36.430D,S36.438A-S36.438D,S36.439A-S36.439D, S36.490A-S36.490D,S36.498A-S36.498D,S36.499A-S36.499D,S36.500A-S36.500D,S36.501A-S36.501D, S36.502A-S36.502D,S36.503A-S36.503D,S36.508A-S36.508D,S36.509A-S36.509D,S36.510A-S36.510D, S36.511A-S36.511D,S36.512A-S36.512D,S36.513A-S36.513D,S36.518A-S36.518D,S36.519A-S36.519D, S36.520A-S36.520D,S36.521A-S36.521D,S36.522A-S36.522D,S36.523A-S36.523D,S36.528A-S36.528D, S36.529A-S36.529D,S36.530A-S36.530D,S36.531A-S36.531D,S36.532A-S36.532D,S36.533A-S36.533D, S36.538A-S36.538D,S36.539A-S36.539D,S36.590A-S36.590D,S36.591A-S36.591D,S36.592A-S36.592D, S36.593A-S36.593D,S36.598A-S36.598D,S36.599A-S36.599D,S36.60XA-S36.60XD,S36.61XA-S36.61XD, S36.62XA-S36.62XD,S36.63XA-S36.63XD,S36.69XA-S36.69XD,S36.81XA-S36.81XD,S36.892A-S36.892D, S36.893A-S36.893D,S36.898A-S36.898D,S36.899A-S36.899D,S36.90XA-S36.90XD,S36.92XA-S36.92XD, S36.93XA-S36.93XD,S36.99XA-S36.99XD,S37.001A-S37.001D,S37.002A-S37.002D,S37.009A-S37.009D, S37.011A-S37.011D,S37.012A-S37.012D,S37.019A-S37.019D,S37.021A-S37.021D,S37.022A-S37.022D, S37.029A-S37.029D,S37.031A-S37.031D,S37.032A-S37.032D,S37.039A-S37.039D,S37.041A-S37.041D, S37.042A-S37.042D,S37.049A-S37.049D,S37.051A-S37.051D,S37.052A-S37.052D,S37.059A-S37.059D, S37.061A-S37.061D,S37.062A-S37.062D,S37.069A-S37.069D,S37.091A-S37.091D,S37.092A-S37.092D, S37.099A-S37.099D,S37.10XA-S37.10XD,S37.12XA-S37.12XD,S37.13XA-S37.13XD,S37.19XA-S37.19XD, S37.20XA-S37.20XD,S37.22XA-S37.22XD,S37.23XA-S37.23XD,S37.29XA-S37.29XD,S37.30XA-S37.30XD, S37.32XA-S37.32XD,S37.33XA-S37.33XD,S37.39XA-S37.39XD,S37.401A-S37.401D,S37.402A-S37.402D, S37.409A-S37.409D,S37.421A-S37.421D,S37.422A-S37.422D,S37.429A-S37.429D,S37.431A-S37.431D, S37.432A-S37.432D,S37.439A-S37.439D,S37.491A-S37.491D,S37.492A-S37.492D,S37.499A-S37.499D, S37.501A-S37.501D,S37.502A-S37.502D,S37.509A-S37.509D,S37.511A-S37.511D,S37.512A-S37.512D, S37.519A-S37.519D,S37.521A-S37.521D,S37.522A-S37.522D,S37.529A-S37.529D,S37.531A-S37.531D, S37.532A-S37.532D,S37.539A-S37.539D,S37.591A-S37.591D,S37.592A-S37.592D,S37.599A-S37.599D, S37.60XA-S37.60XD,S37.62XA-S37.62XD,S37.63XA-S37.63XD,S37.69XA-S37.69XD,S37.812A-S37.812D, S37.813A-S37.813D,S37.818A-S37.818D,S37.819A-S37.819D,S37.822A-S37.822D,S37.823A-S37.823D, S37.828A-S37.828D,S37.829A-S37.829D,S37.892A-S37.892D,S37.893A-S37.893D,S37.898A-S37.898D, S37.899A-S37.899D,S37.90XA-S37.90XD,S37.92XA-S37.92XD,S37.93XA-S37.93XD,S37.99XA-S37.99XD, T79.4XXA-T79.4XXD,T79.7XXA-T79.7XXD

CPT: 31775,31805,32110-32124,32653,32654,32658,32820,33300-33335,34839-34848,37619,39501,39540,39545, 43840,44120-44125,44139-44160,44227,44320,44602-44605,44620-44626,44701,45562,45563,47120-47130, 47350-47362,47533-47537,47802,47900,48545,50220,50546,50693-50695,50740-50760,50947,50948,51102, 51860,51865,52310,52315,52332,53502-53515,58520,93792,93793,97605-97608,98966-98969,99051,99060, 99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **81**
Condition: FRACTURE OF HIP (See Guideline Notes 6,15,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: M84.359A-M84.359G,M84.459A-M84.459G,M84.559A-M84.559G,M84.659A-M84.659G,M91.10-M91.92, S72.001A-S72.001J,S72.002A-S72.002J,S72.009A-S72.009J,S72.011A-S72.011J,S72.012A-S72.012J, S72.019A-S72.019J,S72.021A-S72.021J,S72.022A-S72.022J,S72.023A-S72.023J,S72.024A-S72.024J, S72.025A-S72.025J,S72.026A-S72.026J,S72.031A-S72.031J,S72.032A-S72.032J,S72.033A-S72.033J, S72.034A-S72.034J,S72.035A-S72.035J,S72.036A-S72.036J,S72.041A-S72.041J,S72.042A-S72.042J, S72.043A-S72.043J,S72.044A-S72.044J,S72.045A-S72.045J,S72.046A-S72.046J,S72.051A-S72.051J, S72.052A-S72.052J,S72.059A-S72.059J,S72.061A-S72.061J,S72.062A-S72.062J,S72.063A-S72.063J, S72.064A-S72.064J,S72.065A-S72.065J,S72.066A-S72.066J,S72.091A-S72.091J,S72.092A-S72.092J, S72.099A-S72.099J,S72.101A-S72.101J,S72.102A-S72.102J,S72.109A-S72.109J,S72.111A-S72.111J, S72.112A-S72.112J,S72.113A-S72.113J,S72.114A-S72.114J,S72.115A-S72.115J,S72.116A-S72.116J, S72.121A-S72.121J,S72.122A-S72.122J,S72.123A-S72.123J,S72.124A-S72.124J,S72.125A-S72.125J, S72.126A-S72.126J,S72.131A-S72.131J,S72.132A-S72.132J,S72.133A-S72.133J,S72.134A-S72.134J, S72.135A-S72.135J,S72.136A-S72.136J,S72.141A-S72.141J,S72.142A-S72.142J,S72.143A-S72.143J, S72.144A-S72.144J,S72.145A-S72.145J,S72.146A-S72.146J,S72.21XA-S72.21XJ,S72.22XA-S72.22XJ, S72.23XA-S72.23XJ,S72.24XA-S72.24XJ,S72.25XA-S72.25XJ,S72.26XA-S72.26XJ,S79.001A-S79.001G, S79.002A-S79.002G,S79.009A-S79.009G,S79.011A-S79.011G,S79.012A-S79.012G,S79.019A-S79.019G, S79.091A-S79.091G,S79.092A-S79.092G,S79.099A-S79.099G,Z47.1-Z47.2
CPT: 20680,27125-27132,27230-27248,27254,27267-27269,27506,27656,29035-29046,29305,29325,29700,29710, 29720,77014,77261-77290,77295,77300,77331-77336,77387,77401-77417,77427,77470,93792,93793,97012, 97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line: **82**
Condition: MYOCARDITIS, PERICARDITIS, AND ENDOCARDITIS (See Guideline Notes 18,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: A18.84,A32.82,A39.50-A39.53,A52.03,A52.06,B26.82,B37.6,B57.0,D86.85,I09.0,I09.2,I23.0,I30.0-I30.9,I31.0-I31.9,I32,I33.0-I33.9,I39,I40.0-I40.9,I41,I51.4,I97.0,M32.11-M32.12,Z45.09
CPT: 31750,31760,32659,32661,33010-33050,33361-33391,33405-33413,33418,33419,33425-33465,33475,33477,33530,33946-33966,33969,33975-33993,35820,92960-92971,92978-92998,93355,93750,93792-93798,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9348

Line: **83**
Condition: DEEP OPEN WOUND OF NECK, INCLUDING LARYNX; FRACTURE OF LARYNX OR TRACHEA (See Guideline Notes 64,65)
Treatment: REPAIR
ICD-10: S11.011A-S11.011D,S11.012A-S11.012D,S11.013A-S11.013D,S11.014A-S11.014D,S11.015A-S11.015D,S11.019A-S11.019D,S11.021A-S11.021D,S11.022A-S11.022D,S11.023A-S11.023D,S11.024A-S11.024D,S11.025A-S11.025D,S11.029A-S11.029D,S11.031A-S11.031D,S11.032A-S11.032D,S11.033A-S11.033D,S11.034A-S11.034D,S11.035A-S11.035D,S11.039A-S11.039D,S11.10XA-S11.10XD,S11.11XA-S11.11XD,S11.12XA-S11.12XD,S11.13XA-S11.13XD,S11.14XA-S11.14XD,S11.15XA-S11.15XD,S11.20XA-S11.20XD,S11.21XA-S11.21XD,S11.22XA-S11.22XD,S11.23XA-S11.23XD,S11.24XA-S11.24XD,S11.25XA-S11.25XD,S11.80XA-S11.80XD,S11.81XA-S11.81XD,S11.82XA-S11.82XD,S11.83XA-S11.83XD,S11.84XA-S11.84XD,S11.85XA-S11.85XD,S11.89XA-S11.89XD,S11.90XA-S11.90XD,S11.91XA-S11.91XD,S11.92XA-S11.92XD,S11.93XA-S11.93XD,S11.94XA-S11.94XD,S11.95XA-S11.95XD,S12.8XXA-S12.8XXD,S13.20XA-S13.20XD,S13.29XA-S13.29XD,S16.2XXA-S16.2XXD
CPT: 11010-11012,12001-12007,13131-13133,15004,15005,20100,31528,31529,31584,31630,31766,31780,31781,31800,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **84**
Condition: DIABETES MELLITUS WITH END STAGE RENAL DISEASE (See Coding Specification Below)
Treatment: SIMULTANEOUS PANCREAS/KIDNEY (SPK) TRANSPLANT, PANCREAS AFTER KIDNEY (PAK) TRANSPLANT
ICD-10: E10.21-E10.29,T86.10-T86.19,T86.850-T86.899,Z48.22,Z48.288
CPT: 48160,48550-48556,50300-50365,76776,86825-86835,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2065

SPK included for type I diabetes mellitus with end stage renal disease (E10.2), PAK only included for other type I diabetes mellitus with secondary diagnosis of Z94.0.

Line: **85**
Condition: ENDOCARDIAL CUSHION DEFECTS (See Guideline Notes 64,65)
Treatment: REPAIR
ICD-10: Q20.6-Q20.8,Q21.2,Q21.8-Q21.9
CPT: 33620,33621,33645-33670,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,96154,96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **86**
Condition: CONGENITAL PULMONARY VALVE ATRESIA (See Guideline Notes 64,65)
Treatment: SHUNT/REPAIR
ICD-10: Q22.0
CPT: 33470-33474,33530,33608,33620,33621,33750-33766,33920,33925,33926,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **87**
Condition: CONGENITAL ANOMALIES OF GENITOURINARY SYSTEM (See Guideline Notes 64,65,72)
Treatment: RECONSTRUCTION
ICD-10: Q55.23,Q55.3,Q60.3,Q61.00-Q61.9,Q62.4-Q62.5,Q62.60-Q62.69,Q62.8,Q63.0-Q63.9,Q64.10,Q64.12-Q64.6,Q64.71,Q64.73-Q64.74,Q64.79
CPT: 15002-15005,45820,50040,50045,50100,50125,50135,50220-50290,50390,50400,50405,50540,50542-50546,50548,50553,50572,50605,50650,50722-50728,50760,50780-50785,50825-50860,50947,50948,50970,51020-51045,51080-51597,51715,51800-51980,52214,52290,52300,53020,53025,53080,53085,53210,53215,53400-53460,53621,55175,55180,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **88**
Condition: NECROTIZING ENTEROCOLITIS IN FETUS OR NEWBORN (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: K55.30-K55.33,P77.1-P77.9,Z46.59
CPT: 44120-44125,44130,44139-44160,44300-44320,44340-44346,44602-44605,44620-44650,49442,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **89**
Condition: DISCORDANT CARDIOVASCULAR CONNECTIONS (See Guideline Notes 64,65)
Treatment: REPAIR
ICD-10: Q20.1-Q20.3,Q20.5,Q20.8-Q20.9,Q93.81
CPT: 33418,33419,33611,33612,33620,33621,33684,33735-33766,33770-33783,33946-33966,33969,33984-33989,42225,42226,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **90**
Condition: CONGENITAL MITRAL VALVE STENOSIS/INSUFFICIENCY (See Guideline Notes 64,65)
Treatment: MITRAL VALVE REPAIR/REPLACEMENT
ICD-10: Q23.2-Q23.3,Z79.01
CPT: 33418-33430,33496,33620,33621,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **91**
Condition: GUILLAIN-BARRE SYNDROME (See Guideline Notes 6,64,65)
Treatment: MEDICAL THERAPY
ICD-10: G61.0
CPT: 31600,31610,36514,36516,90284,92507,92508,92521-92526,92607-92609,92633,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9152

Line: **92**
Condition: SEVERE/MODERATE HEAD INJURY: HEMATOMA/EDEMA WITH PERSISTENT SYMPTOMS (See Guideline Notes 6,64,65,90,121)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: S02.0XXA-S02.0XXG,S02.101A-S02.101G,S02.102A-S02.102G,S02.109A-S02.109G,S02.110A-S02.110G,S02.111A-S02.111G,S02.112A-S02.112G,S02.113A-S02.113G,S02.118A-S02.118G,S02.119A-S02.119G,S02.11AA-S02.11AG,S02.11BA-S02.11BG,S02.11CA-S02.11CG,S02.11DA-S02.11DG,S02.11EA-S02.11EG,S02.11FA-S02.11FG,S02.11GA-S02.11GG,S02.11HA-S02.11HG,S02.19XB-S02.19XG,S02.80XA-S02.80XG,S02.81XA-S02.81XG,S02.82XA-S02.82XG,S02.91XA-S02.91XG,S04.041A-S04.041D,S04.042A-S04.042D,S04.049A-S04.049D,S06.0X0A-S06.0X0D,S06.0X1A-S06.0X1D,S06.0X9A-S06.0X9D,S06.1X7A-S06.1X8A,S06.2X0A-S06.2X0D,S06.2X1A-S06.2X1D,S06.2X2A-S06.2X2D,S06.2X3A-S06.2X3D,S06.2X4A-S06.2X4D,S06.2X5A-S06.2X5D,S06.2X6A-S06.2X6D,S06.2X7A-S06.2X9D,S06.300A-S06.300D,S06.301A-S06.301D,S06.302A-S06.302D,S06.303A-S06.303D,S06.304A-S06.304D,S06.305A-S06.305D,S06.306A-S06.306D,S06.307A-S06.309D,S06.310A-S06.310D,S06.311A-S06.311D,S06.312A-S06.312D,S06.313A-S06.313D,S06.314A-S06.314D,S06.315A-S06.315D,S06.316A-S06.316D,S06.317A-S06.319D,S06.320A-S06.320D,S06.321A-S06.321D,S06.322A-S06.322D,S06.323A-S06.323D,S06.324A-S06.324D,S06.325A-S06.325D,

S06.326A-S06.326D,S06.327A-S06.329D,S06.330A-S06.330D,S06.331A-S06.331D,S06.332A-S06.332D, S06.333A-S06.333D,S06.334A-S06.334D,S06.335A-S06.335D,S06.336A-S06.336D,S06.337A-S06.339D, S06.5X8A,S06.6X7A-S06.6X8A
CPT: 11010-11012,11971,21100,21110,61107,61108,61210,61312-61322,61340,61345,61571,62000-62010,62140-62148,92507,92508,92521-92526,92607-92609,92633,93792,93793,96118,96150-96155,97012,97110-97127, 97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239, 99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513-G0515,S9152

Line: **93**
Condition: CHILDHOOD LEUKEMIAS (See Guideline Notes 7,11,12,16,64,65)
Treatment: MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C90.10-C90.12,C91.00-C91.02,C92.00-C92.02,C93.30-C93.32,C95.00-C95.02,D46.20-D46.22,D61.810,G89.3, Z45.49,Z51.0,Z51.12
CPT: 32553,49411,77014,77261-77295,77300-77307,77321-77370,77385-77387,77401-77427,77469,77520-77525, 81246,93792,93793,95990,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480, 99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G6001-G6017,S9537

Line: **94**
Condition: UNDESCENDED TESTICLE (See Guideline Note 72)
Treatment: SURGICAL TREATMENT
ICD-10: Q53.00-Q53.10,Q53.111-Q53.9,Q55.22
CPT: 54512-54522,54550,54560,54620-54660,54690,54692,55200,93792,93793,98966-98969,99051,99060,99070, 99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498, 99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **95**
Condition: HEREDITARY IMMUNE DEFICIENCIES (See Guideline Notes 7,11,14)
Treatment: BONE MARROW TRANSPLANT
ICD-10: D61.810,D81.0-D81.4,D81.6-D81.7,D81.89-D81.9,D82.0-D82.1,T86.01-T86.09,Z48.290,Z52.000-Z52.098,Z52.3
CPT: 36680,38204-38215,38240,38242,38243,86825-86835,90284,93792,93793,96150-96155,96377,96405,96406, 96420-96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239, 99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, S2142,S2150,S9537

Line: **96**
Condition: DIABETIC AND OTHER RETINOPATHY (See Guideline Notes 64,65,116)
Treatment: MEDICAL, SURGICAL, AND LASER TREATMENT
ICD-10: D18.09,E08.311-E08.319,E08.3211-E08.3599,E08.37X1-E08.39,E09.311-E09.319,E09.3211-E09.3599, E09.37X1-E09.39,E10.311-E10.319,E10.3211-E10.3599,E10.37X1-E10.39,E11.311-E11.319,E11.3211-E11.3599, E11.37X1-E11.39,E13.311-E13.319,E13.3211-E13.3599,E13.37X1-E13.39,H31.401-H31.8,H35.021-H35.09, H35.20-H35.23,H35.60-H35.63
CPT: 67027,67028,67036-67043,67208,67210,67220,67227-67229,67515,92002-92014,92018-92060,92081-92136, 92225-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **97**
Condition: BORDERLINE PERSONALITY DISORDER (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F60.3
CPT: 90785,90832-90840,90846,90847,90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239, 99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470, G0508-G0511,G0513,G0514,H0004,H0018,H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,H2033,S5151,S9125,S9480,S9484,T1005

Line: **98**
Condition: HEART FAILURE (See Guideline Notes 18,64,65)
Treatment: MEDICAL THERAPY
ICD-10: I09.81,I27.0-I27.1,I27.20-I27.81,I27.83-I27.9,I50.1,I50.20-I50.43,I50.810-I50.9,I97.110-I97.111,I97.130-I97.191, J81.0-J81.1,P29.0,Z45.09,Z79.01
CPT: 33946-33993,92920-92938,92943,92944,92960-92998,93355,93750,93792-93798,96150-96155,97802-97804, 98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514,S9348

Line: **99**
Condition: CARDIOMYOPATHY (See Guideline Notes 49,64,65,124)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: B57.2,I42.0-I42.9,I43,I51.5,Z45.010-Z45.09,Z79.01
CPT: 21630,33010,33215,33216,33218,33220,33223-33226,33230,33231,33240-33249,33262-33264,33270-33273, 33414-33416,33508-33530,92960-92971,92978-92998,93282-93284,93287,93289,93292,93295,93296,93583, 93644,93724,93745,93792-93798,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0448,G0463-G0467, G0490,G0508-G0511,G0513,G0514,K0606-K0609,S0340-S0342,S9348

Line: **100**
Condition: END STAGE RENAL DISEASE
Treatment: RENAL TRANSPLANT
ICD-10: D30.9,D57.1,D59.3,D69.0,E08.21-E08.29,E09.21-E09.29,E10.21-E10.29,E11.21-E11.29,E13.21-E13.29,E75.21-E75.22,E75.240-E75.249,E75.3,E77.0,E77.8,E78.71-E78.72,I12.0,M30.0-M30.2,M30.8,M31.0,M31.31,M31.7, M32.14-M32.19,M35.04,N00.8,N01.0-N01.9,N02.0-N02.9,N03.0-N03.9,N04.0-N04.9,N05.0-N05.9,N06.0-N06.9, N07.0-N07.9,N08,N11.0-N11.8,N14.0-N14.4,N15.0,N15.8-N15.9,N16,N17.0-N17.9,N18.5-N18.6,N26.1,N26.9, N28.0,Q60.0-Q60.2,Q60.4-Q60.6,Q61.19-Q61.5,Q62.0,Q62.10-Q62.39,Q79.4,Q79.51,Q87.2-Q87.3,Q87.5, Q87.81,Q87.89,Q89.8,T86.10-T86.19,Z48.22,Z52.4
CPT: 36825,36830,50300-50370,50547,52310,76776,86825-86835,93792,93793,96150-96155,98966-98969,99051, 99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490, 99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **101**
Condition: CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: K31.6,P76.0-P76.9,P78.1,P78.81,P78.84-P78.89,Q40.0,Q41.0-Q41.9,Q42.0-Q42.9,Q43.0-Q43.9,Q45.0-Q45.9, T86.890-T86.899,Z46.59
CPT: 31750,31760,32905,32906,39503,39545,43500-43520,43620-43640,43800-43825,43840,43850,43860,43870, 43880,44005,44010,44020,44021,44050,44055,44110-44130,44139-44227,44300-44346,44363-44370,44378, 44379,44381,44384,44391-44402,44404,44405,44408-44701,44715-44721,44800-44955,45000-45020,45108-45123,45130-45150,45303,45308-45320,45327,45333-45335,45338,45340,45346,45347,45381-45389,45393-45397,45800,45905,45910,46040,46045,46060-46080,46270,46275,46604,46610-46614,46705-46754,47300, 47533-47540,47542,47544,47554-47556,47600-47620,47701,47715-47999,48120-48146,48150,48500-48556, 49203-49250,49324,49325,49421-49423,49442,49600-49611,49904,49905,51500,93792,93793,96150-96155, 98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **102**
Condition: HEMOLYTIC DISEASE DUE TO ISOIMMUNIZATION, ANEMIA DUE TO TRANSPLACENTAL HEMORRHAGE, AND FETAL AND NEONATAL JAUNDICE (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: E80.5,P50.0-P50.9,P51.0-P51.9,P55.0-P55.9,P57.0-P57.9,P58.0-P58.3,P58.41-P58.9,P59.0-P59.1,P59.20-P59.9, P61.3-P61.4
CPT: 93792,93793,96900,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404, 99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **103**
Condition: POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS (See Guideline Notes 64,65,156)
Treatment: MEDICAL THERAPY
ICD-10: E67.0,E67.3,P93.0-P93.8,T36.0X1A-T36.0X1D,T36.0X2A-T36.0X2D,T36.0X3A-T36.0X3D,T36.0X4A-T36.0X4D, T36.0X5A-T36.0X5D,T36.1X1A-T36.1X1D,T36.1X2A-T36.1X2D,T36.1X3A-T36.1X3D,T36.1X4A-T36.1X4D, T36.1X5A-T36.1X5D,T36.2X1A-T36.2X1D,T36.2X2A-T36.2X2D,T36.2X3A-T36.2X3D,T36.2X4A-T36.2X4D,

T36.2X5A-T36.2X5D,T36.3X1A-T36.3X1D,T36.3X2A-T36.3X2D,T36.3X3A-T36.3X3D,T36.3X4A-T36.3X4D, T36.3X5A-T36.3X5D,T36.4X1A-T36.4X1D,T36.4X2A-T36.4X2D,T36.4X3A-T36.4X3D,T36.4X4A-T36.4X4D, T36.4X5A-T36.4X5D,T36.5X1A-T36.5X1D,T36.5X2A-T36.5X2D,T36.5X3A-T36.5X3D,T36.5X4A-T36.5X4D, T36.5X5A-T36.5X5D,T36.6X1A-T36.6X1D,T36.6X2A-T36.6X2D,T36.6X3A-T36.6X3D,T36.6X4A-T36.6X4D, T36.6X5A-T36.6X5D,T36.7X1A-T36.7X1D,T36.7X2A-T36.7X2D,T36.7X3A-T36.7X3D,T36.7X4A-T36.7X4D, T36.7X5A-T36.7X5D,T36.8X1A-T36.8X1D,T36.8X2A-T36.8X2D,T36.8X3A-T36.8X3D,T36.8X4A-T36.8X4D, T36.8X5A-T36.8X5D,T36.91XA-T36.91XD,T36.92XA-T36.92XD,T36.93XA-T36.93XD,T36.94XA-T36.94XD, T36.95XA-T36.95XD,T37.0X1A-T37.0X1D,T37.0X2A-T37.0X2D,T37.0X3A-T37.0X3D,T37.0X4A-T37.0X4D, T37.0X5A-T37.0X5D,T37.1X1A-T37.1X1D,T37.1X2A-T37.1X2D,T37.1X3A-T37.1X3D,T37.1X4A-T37.1X4D, T37.1X5A-T37.1X5D,T37.2X1A-T37.2X1D,T37.2X2A-T37.2X2D,T37.2X3A-T37.2X3D,T37.2X4A-T37.2X4D, T37.2X5A-T37.2X5D,T37.3X1A-T37.3X1D,T37.3X2A-T37.3X2D,T37.3X3A-T37.3X3D,T37.3X4A-T37.3X4D, T37.3X5A-T37.3X5D,T37.4X1A-T37.4X1D,T37.4X2A-T37.4X2D,T37.4X3A-T37.4X3D,T37.4X4A-T37.4X4D, T37.4X5A-T37.4X5D,T37.5X1A-T37.5X1D,T37.5X2A-T37.5X2D,T37.5X3A-T37.5X3D,T37.5X4A-T37.5X4D, T37.5X5A-T37.5X5D,T37.8X1A-T37.8X1D,T37.8X2A-T37.8X2D,T37.8X3A-T37.8X3D,T37.8X4A-T37.8X4D, T37.8X5A-T37.8X5D,T37.91XA-T37.91XD,T37.92XA-T37.92XD,T37.93XA-T37.93XD,T37.94XA-T37.94XD, T37.95XA-T37.95XD,T38.0X1A-T38.0X1D,T38.0X2A-T38.0X2D,T38.0X3A-T38.0X3D,T38.0X4A-T38.0X4D, T38.0X5A-T38.0X5D,T38.1X1A-T38.1X1D,T38.1X2A-T38.1X2D,T38.1X3A-T38.1X3D,T38.1X4A-T38.1X4D, T38.1X5A-T38.1X5D,T38.1X6A-T38.1X6D,T38.2X1A-T38.2X1D,T38.2X2A-T38.2X2D,T38.2X3A-T38.2X3D, T38.2X4A-T38.2X4D,T38.2X5A-T38.2X5D,T38.2X6A-T38.2X6D,T38.3X1A-T38.3X1D,T38.3X2A-T38.3X2D, T38.3X3A-T38.3X3D,T38.3X4A-T38.3X4D,T38.3X5A-T38.3X5D,T38.4X1A-T38.4X1D,T38.4X2A-T38.4X2D, T38.4X3A-T38.4X3D,T38.4X4A-T38.4X4D,T38.4X5A-T38.4X5D,T38.5X1A-T38.5X1D,T38.5X2A-T38.5X2D, T38.5X3A-T38.5X3D,T38.5X4A-T38.5X4D,T38.5X5A-T38.5X5D,T38.6X1A-T38.6X1D,T38.6X2A-T38.6X2D, T38.6X3A-T38.6X3D,T38.6X4A-T38.6X4D,T38.6X5A-T38.6X5D,T38.7X1A-T38.7X1D,T38.7X2A-T38.7X2D, T38.7X3A-T38.7X3D,T38.7X4A-T38.7X4D,T38.7X5A-T38.7X5D,T38.801A-T38.801D,T38.802A-T38.802D, T38.803A-T38.803D,T38.804A-T38.804D,T38.805A-T38.805D,T38.811A-T38.811D,T38.812A-T38.812D, T38.813A-T38.813D,T38.814A-T38.814D,T38.815A-T38.815D,T38.891A-T38.891D,T38.892A-T38.892D, T38.893A-T38.893D,T38.894A-T38.894D,T38.895A-T38.895D,T38.901A-T38.901D,T38.902A-T38.902D, T38.903A-T38.903D,T38.904A-T38.904D,T38.905A-T38.905D,T38.991A-T38.991D,T38.992A-T38.992D, T38.993A-T38.993D,T38.994A-T38.994D,T38.995A-T38.995D,T39.011A-T39.011D,T39.012A-T39.012D, T39.013A-T39.013D,T39.014A-T39.014D,T39.015A-T39.015D,T39.091A-T39.091D,T39.092A-T39.092D, T39.093A-T39.093D,T39.094A-T39.094D,T39.095A-T39.095D,T39.1X1A-T39.1X1D,T39.1X2A-T39.1X2D, T39.1X3A-T39.1X3D,T39.1X4A-T39.1X4D,T39.1X5A-T39.1X5D,T39.2X1A-T39.2X1D,T39.2X2A-T39.2X2D, T39.2X3A-T39.2X3D,T39.2X4A-T39.2X4D,T39.2X5A-T39.2X5D,T39.311A-T39.311D,T39.312A-T39.312D, T39.313A-T39.313D,T39.314A-T39.314D,T39.315A-T39.315D,T39.391A-T39.391D,T39.392A-T39.392D, T39.393A-T39.393D,T39.394A-T39.394D,T39.395A-T39.395D,T39.4X1A-T39.4X1D,T39.4X2A-T39.4X2D, T39.4X3A-T39.4X3D,T39.4X4A-T39.4X4D,T39.4X5A-T39.4X5D,T39.8X1A-T39.8X1D,T39.8X2A-T39.8X2D, T39.8X3A-T39.8X3D,T39.8X4A-T39.8X4D,T39.8X5A-T39.8X5D,T39.91XA-T39.91XD,T39.92XA-T39.92XD, T39.93XA-T39.93XD,T39.94XA-T39.94XD,T39.95XA-T39.95XD,T40.0X1A-T40.0X1D,T40.0X2A-T40.0X2D, T40.0X3A-T40.0X3D,T40.0X4A-T40.0X4D,T40.0X5A-T40.0X5D,T40.1X1A-T40.1X1D,T40.1X2A-T40.1X2D, T40.1X3A-T40.1X3D,T40.1X4A-T40.1X4D,T40.2X1A-T40.2X1D,T40.2X2A-T40.2X2D,T40.2X3A-T40.2X3D, T40.2X4A-T40.2X4D,T40.2X5A-T40.2X5D,T40.3X1A-T40.3X1D,T40.3X2A-T40.3X2D,T40.3X3A-T40.3X3D, T40.3X4A-T40.3X4D,T40.3X5A-T40.3X5D,T40.4X1A-T40.4X1D,T40.4X2A-T40.4X2D,T40.4X3A-T40.4X3D, T40.4X4A-T40.4X4D,T40.4X5A-T40.4X5D,T40.5X1A-T40.5X1D,T40.5X2A-T40.5X2D,T40.5X3A-T40.5X3D, T40.5X4A-T40.5X4D,T40.5X5A-T40.5X5D,T40.601A-T40.601D,T40.602A-T40.602D,T40.603A-T40.603D, 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T64.03XA-T64.03XD,T64.04XA-T64.04XD,T64.81XA-T64.81XD,T64.82XA-T64.82XD,T64.83XA-T64.83XD,
T64.84XA-T64.84XD,T65.0X1A-T65.0X1D,T65.0X2A-T65.0X2D,T65.0X3A-T65.0X3D,T65.0X4A-T65.0X4D,
T65.1X1A-T65.1X1D,T65.1X2A-T65.1X2D,T65.1X3A-T65.1X3D,T65.1X4A-T65.1X4D,T65.211A-T65.211D,
T65.212A-T65.212D,T65.213A-T65.213D,T65.214A-T65.214D,T65.221A-T65.221D,T65.222A-T65.222D,
T65.223A-T65.223D,T65.224A-T65.224D,T65.291A-T65.291D,T65.292A-T65.292D,T65.293A-T65.293D,
T65.294A-T65.294D,T65.3X1A-T65.3X1D,T65.3X2A-T65.3X2D,T65.3X3A-T65.3X3D,T65.3X4A-T65.3X4D,
T65.4X1A-T65.4X1D,T65.4X2A-T65.4X2D,T65.4X3A-T65.4X3D,T65.4X4A-T65.4X4D,T65.5X1A-T65.5X1D,
T65.5X2A-T65.5X2D,T65.5X3A-T65.5X3D,T65.5X4A-T65.5X4D,T65.6X1A-T65.6X1D,T65.6X2A-T65.6X2D,
T65.6X3A-T65.6X3D,T65.6X4A-T65.6X4D,T65.811A-T65.811D,T65.812A-T65.812D,T65.813A-T65.813D,
T65.814A-T65.814D,T65.821A-T65.821D,T65.822A-T65.822D,T65.823A-T65.823D,T65.824A-T65.824D,
T65.831A-T65.831D,T65.832A-T65.832D,T65.833A-T65.833D,T65.834A-T65.834D,T65.891A-T65.891D,
T65.892A-T65.892D,T65.893A-T65.893D,T65.894A-T65.894D,T65.91XA-T65.91XD,T65.92XA-T65.92XD,
T65.93XA-T65.93XD,T65.94XA-T65.94XD,T78.41XA-T78.41XD,Z51.6

CPT: 43241,43247,49435,49436,90935-90947,90989-90997,93792,93793,94640,95017,95018,95076,95079,96150-96155,98966-98969,99051,99060,99070,99078,99175,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9355

Line: **104**
Condition: BOTULISM (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A05.1,A48.51-A48.52
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **105**
Condition: TETRALOGY OF FALLOT (TOF); CONGENITAL VENOUS ABNORMALITIES (See Guideline Notes 64,65)
Treatment: REPAIR
ICD-10: Q21.3,Q25.5-Q25.6,Q25.71-Q25.79,Q26.0-Q26.1,Q26.3-Q26.9,Z79.01
CPT: 33606,33608,33620,33621,33692-33697,33726,33735-33750,33764,33917,33924-33926,33946-33966,33969, 33984-33989,34502,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480, 99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line: **106**
Condition: CONGENITAL STENOSIS AND INSUFFICIENCY OF AORTIC VALVE (See Guideline Notes 64,65)
Treatment: SURGICAL VALVE REPLACEMENT/VALVULOPLASTY
ICD-10: Q23.0-Q23.1,Q24.4,Q25.3
CPT: 33361-33417,33496,33530,33620,33621,33946-33966,33969,33984-33989,37246,37247,75557-75565,75573, 92960-92971,92978-92998,93355,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239, 99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line: **107**
Condition: GIANT CELL ARTERITIS, POLYMYALGIA RHEUMATICA AND KAWASAKI DISEASE (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: M30.3,M31.0,M31.4-M31.6,M35.3
CPT: 36514,36516,37609,90284,92002-92014,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078, 99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **108**
Condition: FRACTURE OF RIBS AND STERNUM, OPEN (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: S22.20XB,S22.21XB,S22.22XB,S22.23XB,S22.24XB,S22.31XB,S22.32XB,S22.39XB,S22.41XB,S22.42XB, S22.43XB,S22.49XB,S22.5XXB,S22.9XXB
CPT: 11010-11012,21811-21813,21825,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239, 99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **109**
Condition: SUBACUTE MENINGITIS (E.G., TUBERCULOSIS, CRYPTOCOCCOSIS) (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A01.01,A17.0-A17.1,A17.81-A17.89,A27.81,A42.81-A42.82,B37.5,B45.8,B57.40-B57.49,B58.2,B60.0,G02,G03.0-G03.1,G03.8-G03.9
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **110**
Condition: COAGULATION DEFECTS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: D66-D67,D68.0-D68.2,D68.311-D68.4,D68.8-D68.9,M25.00,M25.011-M25.08,Z14.02
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, S9345

Line: **111**
Condition: CONGENITAL HEART BLOCK; OTHER OBSTRUCTIVE ANOMALIES OF HEART (See Guideline Notes 49,64,65)
Treatment: MEDICAL THERAPY
ICD-10: Q23.8-Q23.9,Q24.6-Q24.8,Q28.8,Z45.010-Z45.09,Z79.01
CPT: 33202-33249,33262-33264,33270-33273,33418-33496,33530,33620,33621,33946-33966,33969,33984-33989, 75557-75565,75573,92960-92971,92978-92998,93279-93284,93286-93289,93292-93296,93355,93644,93745, 93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514,K0606-K0609

Line: **112**
Condition: CANCER OF TESTIS (See Guideline Notes 7,11,12,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C62.00-C62.92,D40.10-D40.12,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.47
CPT: 32553,38564,38571-38573,38780,49327,49411,49412,54512-54535,54660,54690,77261-77290,77295,77300, 77306,77307,77321-77370,77385-77387,77401-77417,77424-77431,77469,77470,93792,93793,96150-96155, 96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G6001-G6017,S9537

Line: **113**
Condition: CANCER OF EYE AND ORBIT (See Guideline Notes 7,11,12,16,19,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C69.00-C69.92,D09.20-D09.22,D48.7,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.840
CPT: 11420,11440,13132,20969,32553,49411,65091,65101-65114,65435,65450,65900,66600,66605,66770,67208-67218,67412,67414,67445,68135,68320-68328,68335,68340,77014,77261-77295,77300-77370,77385-77387, 77401-77432,77469,77470,77520-77525,77750,77789,78816,92002-92014,92018-92060,92081-92136,92225, 92226,92230-92287,93792,93793,96150-96155,96377,96405,96406,96420-96440,96450,96542,96549,96570, 96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449, 99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G6001-G6017,S9537

Line: **114**
Condition: APLASTIC ANEMIAS; AGRANULOCYTOSIS (See Guideline Notes 7,11,12,14)
Treatment: BONE MARROW TRANSPLANT
ICD-10: D60.0-D60.9,D61.01-D61.3,D61.810,D61.82-D61.9,T86.01-T86.09,Z48.290,Z52.000-Z52.008,Z52.090-Z52.098, Z52.3
CPT: 36680,38204-38215,38240,38242,86825,86826,90284,93792,93793,96377,96405,96406,96420-96440,96450, 96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, S2142,S2150,S9537

Line: **115**
Condition: CHRONIC MYELOID LEUKEMIA (See Guideline Notes 7,11,12)
Treatment: MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY, RADIATION AND RADIONUCLEIDE THERAPY
ICD-10: C92.10-C92.32,D61.810,G89.3,Z51.0,Z51.12
CPT: 32553,49411,77014,77261-77290,77295,77300,77306,77307,77321-77370,77385-77387,77401-77417,77424-77427,77469,79101,90284,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570, 96571,98966-98969,99051,99060,99070,99078,99184,99195,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G6001-G6017,S9537

Line: **116**
Condition: HODGKIN'S DISEASE (See Guideline Notes 7,11,12,14,19)
Treatment: BONE MARROW TRANSPLANT
ICD-10: C81.00-C81.99,D61.810,T86.01-T86.09,T86.5,Z48.290,Z52.000-Z52.098,Z52.3,Z85.71
CPT: 36680,38204-38215,38230-38243,78811-78816,86825-86835,90284,93792,93793,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513, G0514,S2142,S2150,S9537

Line: **117**
Condition: FOREIGN BODY IN PHARYNX, LARYNX, TRACHEA, BRONCHUS AND ESOPHAGUS (See Guideline Notes 64,65)
Treatment: REMOVAL OF FOREIGN BODY
ICD-10: T17.200A-T17.200D,T17.208A-T17.208D,T17.210A-T17.210D,T17.220A-T17.220D,T17.228A-T17.228D, T17.290A-T17.290D,T17.298A-T17.298D,T17.300A-T17.300D,T17.308A-T17.308D,T17.310A-T17.310D, T17.320A-T17.320D,T17.328A-T17.328D,T17.390A-T17.390D,T17.398A-T17.398D,T17.400A-T17.400D, T17.408A-T17.408D,T17.410A-T17.410D,T17.418A-T17.418D,T17.420A-T17.420D,T17.428A-T17.428D, T17.490A-T17.490D,T17.498A-T17.498D,T17.500A-T17.500D,T17.508A-T17.508D,T17.510A-T17.510D, T17.518A-T17.518D,T17.520A-T17.520D,T17.528A-T17.528D,T17.590A-T17.590D,T17.598A-T17.598D, T17.800A-T17.800D,T17.808A-T17.808D,T17.810A-T17.810D,T17.820A-T17.820D,T17.828A-T17.828D, T17.890A-T17.890D,T17.898A-T17.898D,T17.900A-T17.900D,T17.908A-T17.908D,T17.910A-T17.910D, T17.920A-T17.920D,T17.928A-T17.928D,T17.990A-T17.990D,T17.998A-T17.998D,T18.0XXA-T18.0XXD, T18.100A-T18.100D,T18.108A-T18.108D,T18.110A-T18.110D,T18.120A-T18.120D,T18.128A-T18.128D, T18.190A-T18.190D,T18.198A-T18.198D
CPT: 31511,31512,31530,31531,31635,32150,32151,40804,41805,42809,43020,43045,43194,43215,43247,43249, 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **118**
Condition: NUTRITIONAL DEFICIENCIES (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: D50.0-D50.9,D51.0-D51.9,D52.0-D52.9,D53.0-D53.9,D64.0-D64.3,D81.818-D81.819,E40-E43,E44.0-E44.1,E45-E46,E50.0-E50.9,E51.11-E51.12,E51.8-E51.9,E52,E53.0-E53.9,E54,E55.0-E55.9,E56.0-E56.8,E58-E60,E61.0-E61.6,E63.0-E63.8
CPT: 93792,93793,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99468,99469,99477-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **119**
Condition: ATRIAL SEPTAL DEFECT, SECUNDUM (See Guideline Notes 64,65)
Treatment: REPAIR SEPTAL DEFECT
ICD-10: Q21.1
CPT: 33641,33647,33946-33966,33969,33984-33989,92960-92971,92978-92998,93355,93580,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480, 99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line: **120**
Condition: CHOANAL ATRESIA (See Guideline Notes 64,65)
Treatment: REPAIR OF CHOANAL ATRESIA
ICD-10: Q30.0
CPT: 30520-30545,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **121**
Condition: ABUSE AND NEGLECT (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: T73.0XXA-T73.0XXD,T73.1XXA-T73.1XXD,T74.01XA-T74.01XD,T74.02XA-T74.02XD,T74.11XA-T74.11XD, T74.12XA-T74.12XD,T74.21XA-T74.21XD,T74.22XA-T74.22XD,T74.31XA-T74.31XD,T74.32XA-T74.32XD, T74.4XXA-T74.4XXD,T74.91XA-T74.91XD,T74.92XA-T74.92XD,T76.01XA-T76.01XD,T76.02XA-T76.02XD, T76.11XA-T76.11XD,T76.12XA-T76.12XD,T76.21XA-T76.21XD,T76.22XA-T76.22XD,T76.31XA-T76.31XD, T76.32XA-T76.32XD,T76.91XA-T76.91XD,T76.92XA-T76.92XD,Z04.41-Z04.42,Z04.71-Z04.72,Z69.010-Z69.020, Z69.11,Z69.81
CPT: 46700,46706,46707,56800,56810,57023,57200,57210,57415,90785,90832-90840,90846-90853,90882,90887, 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, H0038,H2027

Line: **122**
Condition: ATTENTION DEFICIT/HYPERACTIVITY DISORDERS (See Guideline Notes 20,64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F90.0-F90.9
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224, 99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513, G0514,H0004,H0023,H0032-H0038,H0045,H2010,H2012-H2014,H2021,H2022,H2027,H2032,S5151,S9125, S9484,T1005

Line: **123**
Condition: MALARIA, CHAGAS' DISEASE AND TRYPANOSOMIASIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: B50.0-B50.9,B51.8-B51.9,B52.0-B52.9,B53.0-B53.8,B54,B56.0-B56.9,B57.1,B57.30-B57.39,B57.5
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **124**
Condition: ANAPHYLACTIC SHOCK; EDEMA OF LARYNX (See Guideline Notes 64,65,156)
Treatment: MEDICAL THERAPY
ICD-10: J38.4,T78.00XA-T78.00XD,T78.01XA-T78.01XD,T78.02XA-T78.02XD,T78.03XA-T78.03XD,T78.04XA-T78.04XD, T78.05XA-T78.05XD,T78.06XA-T78.06XD,T78.07XA-T78.07XD,T78.08XA-T78.08XD,T78.09XA-T78.09XD, T78.2XXA-T78.2XXD,T88.2XXA-T88.2XXD,T88.6XXA-T88.6XXD,Z51.6
CPT: 86003,86008,86486,93792,93793,95004,95017-95180,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **125**
Condition: THYROTOXICOSIS WITH OR WITHOUT GOITER, ENDOCRINE EXOPHTHALMOS; CHRONIC THYROIDITIS (See Guideline Notes 12,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT WHICH INCLUDES RADIATION THERAPY
ICD-10: E05.00-E05.91,E06.0-E06.9,Z51.0
CPT: 32553,36514,36516,49411,60210-60240,60270,60271,60512,67414,67440,67445,77014,77261-77295,77300-77307,77331-77338,77385-77387,77401-77427,77469,77470,79005-79445,92002-92014,92081,92082,93792, 93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449, 99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G6001-G6017

Line: **126**
Condition: BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD (See Guideline Notes 7,11,16,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: D18.02,D32.0-D32.9,D33.0-D33.7,D35.2-D35.3,D44.3-D44.4,D61.810,G89.3,H47.141-H47.149,Q85.00-Q85.09, Q85.8-Q85.9,Z45.49,Z51.0,Z51.12,Z86.011
CPT: 12034,32553,49411,61312-61330,61333-61512,61516-61521,61524-61530,61534,61536-61564,61571-61626, 61781,61782,61796-61800,62100,62140-62160,62163-62165,62223,62272,63265,63275-63295,63615,77014, 77261-77295,77300-77307,77321-77372,77385-77387,77402-77432,77469,77470,77520-77763,77770-77790, 79005-79445,92002-92014,92081-92083,93792,93793,95990,96150-96155,96377,96405,96406,96420-96440, 96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285, 99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G6001-G6017

Line: **127**
Condition: ACUTE KIDNEY INJURY (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY INCLUDING DIALYSIS
ICD-10: N00.0-N00.9,N01.0-N01.9,N17.0-N17.9,Z49.01-Z49.32
CPT: 36514,36516,36818-36821,36831-36838,36901-36909,49324-49326,49421,49422,49435,49436,90935-90947, 90989-90997,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, S9339,S9537

Line: **128**
Condition: COMMON TRUNCUS (See Guideline Notes 64,65)
Treatment: TOTAL REPAIR/REPLANT ARTERY
ICD-10: Q20.0
CPT: 33608,33620,33621,33786,33788,33813,33814,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **129**
Condition: GRANULOMATOSIS WITH POLYANGIITIS (See Guideline Notes 12,16,64,65)
Treatment: MEDICAL THERAPY, WHICH INCLUDES RADIATION THERAPY
ICD-10: G89.3,M30.1,M31.2,M31.30-M31.31,M31.7,Z51.0
CPT: 32553,36514,36516,49411,77014,77261-77295,77300-77307,77331-77338,77385-77387,77401-77427,77469,77470,77520-77525,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017

Line: **130**
Condition: TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION (See Guideline Notes 14,64,65)
Treatment: COMPLETE REPAIR
ICD-10: Q24.2,Q26.2
CPT: 33620,33621,33724,33730,33732,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **131**
Condition: CRUSH INJURIES OTHER THAN DIGITS; COMPARTMENT SYNDROME (See Guideline Notes 6,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: M60.000-M60.005,M60.011-M60.09,M62.82,M79.A11-M79.A9,S07.0XXA-S07.0XXD,S07.1XXA-S07.1XXD,S07.8XXA-S07.8XXD,S07.9XXA-S07.9XXD,S17.0XXA-S17.0XXD,S17.8XXA-S17.8XXD,S17.9XXA-S17.9XXD,S28.0XXA-S28.0XXD,S35.8X1A-S35.8X1D,S35.8X8A-S35.8X8D,S35.8X9A-S35.8X9D,S35.90XA-S35.90XD,S35.91XA-S35.91XD,S35.99XA-S35.99XD,S38.001A-S38.001D,S38.002A-S38.002D,S38.01XA-S38.01XD,S38.02XA-S38.02XD,S38.03XA-S38.03XD,S38.1XXA-S38.1XXD,S47.1XXA-S47.1XXD,S47.2XXA-S47.2XXD,S47.9XXA-S47.9XXD,S57.00XA-S57.00XD,S57.01XA-S57.01XD,S57.02XA-S57.02XD,S57.80XA-S57.80XD,S57.81XA-S57.81XD,S57.82XA-S57.82XD,S67.20XA-S67.20XD,S67.21XA-S67.21XD,S67.22XA-S67.22XD,S67.30XA-S67.30XD,S67.31XA-S67.31XD,S67.32XA-S67.32XD,S67.40XA-S67.40XD,S67.41XA-S67.41XD,S67.42XA-S67.42XD,S67.90XA-S67.90XD,S67.91XA-S67.91XD,S67.92XA-S67.92XD,S77.00XA-S77.00XD,S77.01XA-S77.01XD,S77.02XA-S77.02XD,S77.10XA-S77.10XD,S77.11XA-S77.11XD,S77.12XA-S77.12XD,S77.20XA-S77.20XD,S77.21XA-S77.21XD,S77.22XA-S77.22XD,S87.00XA-S87.00XD,S87.01XA-S87.01XD,S87.02XA-S87.02XD,S87.80XA-S87.80XD,S87.81XA-S87.81XD,S87.82XA-S87.82XD,S97.00XA-S97.00XD,S97.01XA-S97.01XD,S97.02XA-S97.02XD,S97.80XA-S97.80XD,S97.81XA-S97.81XD,S97.82XA-S97.82XD,T79.5XXA-T79.5XXD,T79.6XXA-T79.6XXD,T79.A0XA-T79.A0XD,T79.A11A-T79.A11D,T79.A12A-T79.A12D,T79.A19A-T79.A19D,T79.A21A-T79.A21D,T79.A22A-T79.A22D,T79.A29A-T79.A29D,T79.A3XA-T79.A3XD,T79.A9XA-T79.A9XD,T79.8XXA-T79.8XXD,T79.9XXA-T79.9XXD
CPT: 11043-11047,11740,20101-20103,20950,20972,21627,21630,23395,24495,25020-25025,25274,25295,25320,25335,25337,25390-25393,25441-25447,25450-25492,25810-25830,26037,26357-26390,26437,27025,27027,27057,27305,27465-27468,27496-27499,27600-27602,27656-27659,27665,27695-27698,27892-27894,28008,35141,35221,36514,36516,37616,37617,54230,74445,92960-92971,92978-92998,93792-93798,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **132**
Condition: OPEN FRACTURE/DISLOCATION OF EXTREMITIES (See Guideline Notes 6,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: S42.001B,S42.002B,S42.009B,S42.011B,S42.012B,S42.013B,S42.014B,S42.015B,S42.016B,S42.017B,S42.018B,S42.019B,S42.021B,S42.022B,S42.023B,S42.024B,S42.025B,S42.026B,S42.031B,S42.032B,S42.033B,S42.034B,S42.035B,S42.036B,S42.101B,S42.102B,S42.109B,S42.111B,S42.112B,S42.113B,S42.114B,S42.115B,S42.116B,S42.121B,S42.122B,S42.123B,S42.124B,S42.125B,S42.126B,S42.131B,S42.132B,S42.133B,S42.134B,S42.135B,S42.136B,S42.141B,S42.142B,S42.143B,S42.144B,S42.145B,S42.146B,S42.151B,S42.152B,S42.153B,S42.154B,S42.155B,S42.156B,S42.191B,S42.192B,S42.199B,S42.201B,S42.202B,S42.209B,S42.211B,S42.212B,S42.213B,S42.214B,S42.215B,S42.216B,S42.221B,S42.222B,S42.223B,S42.224B,S42.225B,S42.226B,S42.231B,S42.232B,S42.239B,S42.241B,S42.242B,

S42.249B,S42.251B,S42.252B,S42.253B,S42.254B,S42.255B,S42.256B,S42.261B,S42.262B,S42.263B,
S42.264B,S42.265B,S42.266B,S42.291B,S42.292B,S42.293B,S42.294B,S42.295B,S42.296B,S42.301B,
S42.302B,S42.309B,S42.321B,S42.322B,S42.323B,S42.324B,S42.325B,S42.326B,S42.331B,S42.332B,
S42.333B,S42.334B,S42.335B,S42.336B,S42.341B,S42.342B,S42.343B,S42.344B,S42.345B,S42.346B,
S42.351B,S42.352B,S42.353B,S42.354B,S42.355B,S42.356B,S42.361B,S42.362B,S42.363B,S42.364B,
S42.365B,S42.366B,S42.391B,S42.392B,S42.399B,S42.401B,S42.402B,S42.409B,S42.411B,S42.412B,
S42.413B,S42.414B,S42.415B,S42.416B,S42.421B,S42.422B,S42.423B,S42.424B,S42.425B,S42.426B,
S42.431B,S42.432B,S42.433B,S42.434B,S42.435B,S42.436B,S42.441B,S42.442B,S42.443B,S42.444B,
S42.445B,S42.446B,S42.447B,S42.448B,S42.449B,S42.451B,S42.452B,S42.453B,S42.454B,S42.455B,
S42.456B,S42.461B,S42.462B,S42.463B,S42.464B,S42.465B,S42.466B,S42.471B,S42.472B,S42.473B,
S42.474B,S42.475B,S42.476B,S42.491B,S42.492B,S42.493B,S42.494B,S42.495B,S42.496B,S42.90XB,
S42.91XB,S42.92XB,S52.001B-S52.001C,S52.001E-S52.001F,S52.001H-S52.001J,S52.002B-S52.002C,
S52.002E-S52.002F,S52.002H-S52.002J,S52.009B-S52.009C,S52.009E-S52.009F,S52.009H-S52.009J,
S52.021B-S52.021C,S52.021E-S52.021F,S52.021H-S52.021J,S52.022B-S52.022C,S52.022E-S52.022F,
S52.022H-S52.022J,S52.023B-S52.023C,S52.023E-S52.023F,S52.023H-S52.023J,S52.024B-S52.024C,
S52.024E-S52.024F,S52.024H-S52.024J,S52.025B-S52.025C,S52.025E-S52.025F,S52.025H-S52.025J,
S52.026B-S52.026C,S52.026E-S52.026F,S52.026H-S52.026J,S52.031B-S52.031C,S52.031E-S52.031F,
S52.031H-S52.031J,S52.032B-S52.032C,S52.032E-S52.032F,S52.032H-S52.032J,S52.033B-S52.033C,
S52.033E-S52.033F,S52.033H-S52.033J,S52.034B-S52.034C,S52.034E-S52.034F,S52.034H-S52.034J,
S52.035B-S52.035C,S52.035E-S52.035F,S52.035H-S52.035J,S52.036B-S52.036C,S52.036E-S52.036F,
S52.036H-S52.036J,S52.041B-S52.041C,S52.041E-S52.041F,S52.041H-S52.041J,S52.042B-S52.042C,
S52.042E-S52.042F,S52.042H-S52.042J,S52.043B-S52.043C,S52.043E-S52.043F,S52.043H-S52.043J,
S52.044B-S52.044C,S52.044E-S52.044F,S52.044H-S52.044J,S52.045B-S52.045C,S52.045E-S52.045F,
S52.045H-S52.045J,S52.046B-S52.046C,S52.046E-S52.046F,S52.046H-S52.046J,S52.091B-S52.091C,
S52.091E-S52.091F,S52.091H-S52.091J,S52.092B-S52.092C,S52.092E-S52.092F,S52.092H-S52.092J,
S52.099B-S52.099C,S52.099E-S52.099F,S52.099H-S52.099J,S52.101B-S52.101C,S52.101E-S52.101F,
S52.101H-S52.101J,S52.102B-S52.102C,S52.102E-S52.102F,S52.102H-S52.102J,S52.109B-S52.109C,
S52.109E-S52.109F,S52.109H-S52.109J,S52.121B-S52.121C,S52.121E-S52.121F,S52.121H-S52.121J,
S52.122B-S52.122C,S52.122E-S52.122F,S52.122H-S52.122J,S52.123B-S52.123C,S52.123E-S52.123F,
S52.123H-S52.123J,S52.124B-S52.124C,S52.124E-S52.124F,S52.124H-S52.124J,S52.125B-S52.125C,
S52.125E-S52.125F,S52.125H-S52.125J,S52.126B-S52.126C,S52.126E-S52.126F,S52.126H-S52.126J,
S52.131B-S52.131C,S52.131E-S52.131F,S52.131H-S52.131J,S52.132B-S52.132C,S52.132E-S52.132F,
S52.132H-S52.132J,S52.133B-S52.133C,S52.133E-S52.133F,S52.133H-S52.133J,S52.134B-S52.134C,
S52.134E-S52.134F,S52.134H-S52.134J,S52.135B-S52.135C,S52.135E-S52.135F,S52.135H-S52.135J,
S52.136B-S52.136C,S52.136E-S52.136F,S52.136H-S52.136J,S52.181B-S52.181C,S52.181E-S52.181F,
S52.181H-S52.181J,S52.182B-S52.182C,S52.182E-S52.182F,S52.182H-S52.182J,S52.189B-S52.189C,
S52.189E-S52.189F,S52.189H-S52.189J,S52.201B-S52.201C,S52.201E-S52.201F,S52.201H-S52.201J,
S52.202B-S52.202C,S52.202E-S52.202F,S52.202H-S52.202J,S52.209B-S52.209C,S52.209E-S52.209F,
S52.209H-S52.209J,S52.221B-S52.221C,S52.221E-S52.221F,S52.221H-S52.221J,S52.222B-S52.222C,
S52.222E-S52.222F,S52.222H-S52.222J,S52.223B-S52.223C,S52.223E-S52.223F,S52.223H-S52.223J,
S52.224B-S52.224C,S52.224E-S52.224F,S52.224H-S52.224J,S52.225B-S52.225C,S52.225E-S52.225F,
S52.225H-S52.225J,S52.226B-S52.226C,S52.226E-S52.226F,S52.226H-S52.226J,S52.231B-S52.231C,
S52.231E-S52.231F,S52.231H-S52.231J,S52.232B-S52.232C,S52.232E-S52.232F,S52.232H-S52.232J,
S52.233B-S52.233C,S52.233E-S52.233F,S52.233H-S52.233J,S52.234B-S52.234C,S52.234E-S52.234F,
S52.234H-S52.234J,S52.235B-S52.235C,S52.235E-S52.235F,S52.235H-S52.235J,S52.236B-S52.236C,
S52.236E-S52.236F,S52.236H-S52.236J,S52.241B-S52.241C,S52.241E-S52.241F,S52.241H-S52.241J,
S52.242B-S52.242C,S52.242E-S52.242F,S52.242H-S52.242J,S52.243B-S52.243C,S52.243E-S52.243F,
S52.243H-S52.243J,S52.244B-S52.244C,S52.244E-S52.244F,S52.244H-S52.244J,S52.245B-S52.245C,
S52.245E-S52.245F,S52.245H-S52.245J,S52.246B-S52.246C,S52.246E-S52.246F,S52.246H-S52.246J,
S52.251B-S52.251C,S52.251E-S52.251F,S52.251H-S52.251J,S52.252B-S52.252C,S52.252E-S52.252F,
S52.252H-S52.252J,S52.253B-S52.253C,S52.253E-S52.253F,S52.253H-S52.253J,S52.254B-S52.254C,
S52.254E-S52.254F,S52.254H-S52.254J,S52.255B-S52.255C,S52.255E-S52.255F,S52.255H-S52.255J,
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S82.492C,S82.492E-S82.492F,S82.492H-S82.492J,S82.499B-S82.499C,S82.499E-S82.499F,S82.499H-
S82.499J,S82.51XB-S82.51XC,S82.51XE-S82.51XF,S82.51XH-S82.51XJ,S82.52XB-S82.52XC,S82.52XE-
S82.52XF,S82.52XH-S82.52XJ,S82.53XB-S82.53XC,S82.53XE-S82.53XF,S82.53XH-S82.53XJ,S82.54XB-
S82.54XC,S82.54XE-S82.54XF,S82.54XH-S82.54XJ,S82.55XB-S82.55XC,S82.55XE-S82.55XF,S82.55XH-
S82.55XJ,S82.56XB-S82.56XC,S82.56XE-S82.56XF,S82.56XH-S82.56XJ,S82.61XB-S82.61XC,S82.61XE-
S82.61XF,S82.61XH-S82.61XJ,S82.62XB-S82.62XC,S82.62XE-S82.62XF,S82.62XH-S82.62XJ,S82.63XB-
S82.63XC,S82.63XE-S82.63XF,S82.63XH-S82.63XJ,S82.64XB-S82.64XC,S82.64XE-S82.64XF,S82.64XH-
S82.64XJ,S82.65XB-S82.65XC,S82.65XE-S82.65XF,S82.65XH-S82.65XJ,S82.66XB-S82.66XC,S82.66XE-
S82.66XF,S82.66XH-S82.66XJ,S82.831B-S82.831C,S82.831E-S82.831F,S82.831H-S82.831J,S82.832B-
S82.832C,S82.832E-S82.832F,S82.832H-S82.832J,S82.839B-S82.839C,S82.839E-S82.839F,S82.839H-
S82.839J,S82.841B-S82.841C,S82.841E-S82.841F,S82.841H-S82.841J,S82.842B-S82.842C,S82.842E-
S82.842F,S82.842H-S82.842J,S82.843B-S82.843C,S82.843E-S82.843F,S82.843H-S82.843J,S82.844B-
S82.844C,S82.844E-S82.844F,S82.844H-S82.844J,S82.845B-S82.845C,S82.845E-S82.845F,S82.845H-

S82.845J,S82.846B-S82.846C,S82.846E-S82.846F,S82.846H-S82.846J,S82.851B-S82.851C,S82.851E-S82.851F,S82.851H-S82.851J,S82.852B-S82.852C,S82.852E-S82.852F,S82.852H-S82.852J,S82.853B-S82.853C,S82.853E-S82.853F,S82.853H-S82.853J,S82.854B-S82.854C,S82.854E-S82.854F,S82.854H-S82.854J,S82.855B-S82.855C,S82.855E-S82.855F,S82.855H-S82.855J,S82.856B-S82.856C,S82.856E-S82.856F,S82.856H-S82.856J,S82.861B-S82.861C,S82.861E-S82.861F,S82.861H-S82.861J,S82.862B-S82.862C,S82.862E-S82.862F,S82.862H-S82.862J,S82.863B-S82.863C,S82.863E-S82.863F,S82.863H-S82.863J,S82.864B-S82.864C,S82.864E-S82.864F,S82.864H-S82.864J,S82.865B-S82.865C,S82.865E-S82.865F,S82.865H-S82.865J,S82.866B-S82.866C,S82.866E-S82.866F,S82.866H-S82.866J,S82.871B-S82.871C,S82.871E-S82.871F,S82.871H-S82.871J,S82.872B-S82.872C,S82.872E-S82.872F,S82.872H-S82.872J,S82.873B-S82.873C,S82.873E-S82.873F,S82.873H-S82.873J,S82.874B-S82.874C,S82.874E-S82.874F,S82.874H-S82.874J,S82.875B-S82.875C,S82.875E-S82.875F,S82.875H-S82.875J,S82.876B-S82.876C,S82.876E-S82.876F,S82.876H-S82.876J,S82.891B-S82.891C,S82.891E-S82.891F,S82.891H-S82.891J,S82.892B-S82.892C,S82.892E-S82.892F,S82.892H-S82.892J,S82.899B-S82.899C,S82.899E-S82.899F,S82.899H-S82.899J,S82.90XB-S82.90XC,S82.90XE-S82.90XF,S82.90XH-S82.90XJ,S82.91XB-S82.91XC,S82.91XE-S82.91XF,S82.91XH-S82.91XJ,S82.92XB-S82.92XC,S82.92XE-S82.92XF,S82.92XH-S82.92XJ,S92.001B,S92.002B,S92.009B,S92.011B,S92.012B,S92.013B,S92.014B,S92.015B,S92.016B,S92.021B,S92.022B,S92.023B,S92.024B,S92.025B,S92.026B,S92.031B,S92.032B,S92.033B,S92.034B,S92.035B,S92.036B,S92.041B,S92.042B,S92.043B,S92.044B,S92.045B,S92.046B,S92.051B,S92.052B,S92.053B,S92.054B,S92.055B,S92.056B,S92.061B,S92.062B,S92.063B,S92.064B,S92.065B,S92.066B,S92.101B,S92.102B,S92.109B,S92.111B,S92.112B,S92.113B,S92.114B,S92.115B,S92.116B,S92.121B,S92.122B,S92.123B,S92.124B,S92.125B,S92.126B,S92.131B,S92.132B,S92.133B,S92.134B,S92.135B,S92.136B,S92.141B,S92.142B,S92.143B,S92.144B,S92.145B,S92.146B,S92.151B,S92.152B,S92.153B,S92.154B,S92.155B,S92.156B,S92.191B,S92.192B,S92.199B,S92.201B,S92.202B,S92.209B,S92.211B,S92.212B,S92.213B,S92.214B,S92.215B,S92.216B,S92.221B,S92.222B,S92.223B,S92.224B,S92.225B,S92.226B,S92.231B,S92.232B,S92.233B,S92.234B,S92.235B,S92.236B,S92.241B,S92.242B,S92.243B,S92.244B,S92.245B,S92.246B,S92.251B,S92.252B,S92.253B,S92.254B,S92.255B,S92.256B,S92.301B,S92.302B,S92.309B,S92.311B,S92.312B,S92.313B,S92.314B,S92.315B,S92.316B,S92.321B,S92.322B,S92.323B,S92.324B,S92.325B,S92.326B,S92.331B,S92.332B,S92.333B,S92.334B,S92.335B,S92.336B,S92.341B,S92.342B,S92.343B,S92.344B,S92.345B,S92.346B,S92.351B,S92.352B,S92.353B,S92.354B,S92.355B,S92.356B,S92.401B,S92.402B,S92.403B,S92.404B,S92.405B,S92.406B,S92.411B,S92.412B,S92.413B,S92.414B,S92.415B,S92.416B,S92.421B,S92.422B,S92.423B,S92.424B,S92.425B,S92.426B,S92.491B,S92.492B,S92.499B,S92.501B,S92.502B,S92.503B,S92.504B,S92.505B,S92.506B,S92.511B,S92.512B,S92.513B,S92.514B,S92.515B,S92.516B,S92.521B,S92.522B,S92.523B,S92.524B,S92.525B,S92.526B,S92.531B,S92.532B,S92.533B,S92.534B,S92.535B,S92.536B,S92.591B,S92.592B,S92.599B,S92.811B,S92.812B,S92.819B,S92.901B,S92.902B,S92.909B,S92.911B,S92.912B,S92.919B,S99.001B,S99.002B,S99.009B,S99.011B,S99.012B,S99.019B,S99.021B,S99.022B,S99.029B,S99.031B,S99.032B,S99.039B,S99.041B,S99.042B,S99.049B,S99.091B,S99.092B,S99.099B,S99.101B,S99.102B,S99.109B,S99.111B,S99.112B,S99.119B,S99.121B,S99.122B,S99.129B,S99.131B,S99.132B,S99.139B,S99.141B,S99.142B,S99.149B,S99.191B,S99.192B,S99.199B,S99.201B,S99.202B,S99.209B,S99.211B,S99.212B,S99.219B,S99.221B,S99.222B,S99.229B,S99.231B,S99.232B,S99.239B,S99.241B,S99.242B,S99.249B,S99.291B,S99.292B,S99.299B,Z47.2

CPT: 11010-11012,11740,11760,12001-12020,12031-12057,20150,20650,20663,20670-20694,21485,21490,22848,23395,23400,23515,23530,23532,23550,23552,23585,23615,23630,23660,23670,23680,24130,24300,24332,24343,24345,24346,24515,24516,24545,24546,24575,24579,24586,24587,24615,24635,24640,24665,24666,24685,25119,25210-25240,25275,25310,25320,25337,25390-25392,25394,25430,25431,25441-25447,25450-25492,25515,25525,25526,25545,25574,25575,25606-25609,25628,25645,25652,25670,25676,25685,25695,25810-25825,26340,26615,26645,26665,26685,26686,26715,26727,26735,26746,26756,26765,26775-26785,26910,27235,27244,27248,27253-27258,27275,27350,27430,27435,27465-27468,27502,27506,27507,27511-27514,27519,27524,27535,27536,27540,27556-27566,27610,27656,27695-27698,27712,27756-27759,27766,27769,27784,27792,27814,27822-27832,27846,27848,28415,28420,28445,28465,28485,28505,28525,28531-28675,28730,29035-29105,29126-29131,29305-29445,29505,29515,29700-29720,29850-29856,29861-29863,29871,29874-29879,29882,29888-29898,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **133**
Condition: CANCER OF CERVIX (See Guideline Notes 7,11,12,19,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C53.0-C53.9,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.41
CPT: 32553,38562,38564,38571-38573,38770,44188,44320,44700,49327,49411,49412,53444,55920,57155,57156,57505,57520,57522,57531-57550,57558,58150,58200,58210,58260,58548-58554,58570-58575,58953-58956,77014,77261-77295,77300-77370,77385-77387,77402-77417,77424-77431,77469,77470,77761-77763,77770-77790,78811-78816,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

Line: 134
Condition: INTERRUPTED AORTIC ARCH (See Guideline Notes 64,65)
Treatment: TRANSVERSE ARCH GRAFT
ICD-10: Q25.21-Q25.29,Q25.40-Q25.42,Q25.49
CPT: 33608,33852,33853,33870,33946-33966,33969,33984-33989,92960-92971,92978-92998,93355,93792-93798, 98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line: 135
Condition: HODGKIN'S DISEASE (See Guideline Notes 7,11,12,19,64,65)
Treatment: MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C81.00-C81.99,D61.810,G89.3,Z51.0,Z51.12,Z85.71
CPT: 32553,38100,38120,49203-49205,49220,49411,77014,77261-77295,77300-77307,77321-77370,77385-77387, 77401-77427,77469,77470,78811-78816,79403,93792,93793,96150-96155,96377,96405,96406,96420-96450, 96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513, G0514,G6001-G6017,S9537

Line: 136
Condition: TRAUMATIC AMPUTATION OF LEG(S) (COMPLETE)(PARTIAL) WITH AND WITHOUT COMPLICATION (See Guideline Notes 6,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: S78.011A-S78.011D,S78.012A-S78.012D,S78.019A-S78.019D,S78.021A-S78.021D,S78.022A-S78.022D, S78.029A-S78.029D,S78.111A-S78.111D,S78.112A-S78.112D,S78.119A-S78.119D,S78.121A-S78.121D, S78.122A-S78.122D,S78.129A-S78.129D,S78.911A-S78.911D,S78.912A-S78.912D,S78.919A-S78.919D, S78.921A-S78.921D,S78.922A-S78.922D,S78.929A-S78.929D,S88.011A-S88.011D,S88.012A-S88.012D, S88.019A-S88.019D,S88.021A-S88.021D,S88.022A-S88.022D,S88.029A-S88.029D,S88.111A-S88.111D, S88.112A-S88.112D,S88.119A-S88.119D,S88.121A-S88.121D,S88.122A-S88.122D,S88.129A-S88.129D, S88.911A-S88.911D,S88.912A-S88.912D,S88.919A-S88.919D,S88.921A-S88.921D,S88.922A-S88.922D, S88.929A-S88.929D
CPT: 11010-11012,27290,27295,27590-27598,27880-27886,27889,93792,93793,96150-96155,97012,97110-97124, 97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239, 99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513,G0514

Line: 137
Condition: OPPORTUNISTIC INFECTIONS IN IMMUNOCOMPROMISED HOSTS; CANDIDIASIS OF STOMA; PERSONS RECEIVING CONTINUOUS ANTIBIOTIC THERAPY (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A02.9,B00.1,B35.0,B35.2-B35.9,B36.1,B37.0,B37.41-B37.49,B37.83,B45.8,B59
CPT: 11720,11721,17110,17111,92002-92014,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078, 99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 138
Condition: EBSTEIN'S ANOMALY (See Guideline Notes 64,65)
Treatment: REPAIR SEPTAL DEFECT/VALVULOPLASTY/REPLACEMENT
ICD-10: Q22.5
CPT: 33460,33465,33468,33620,33621,33641-33647,33946-33966,33969,33984-33989,75557-75565,75573,93355, 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 139
Condition: GLAUCOMA, OTHER THAN PRIMARY ANGLE-CLOSURE (See Guideline Notes 64,65)
Treatment: MEDICAL, SURGICAL AND LASER TREATMENT
ICD-10: H40.001-H40.029,H40.041-H40.059,H40.10X0-H40.159,H40.30X0-H40.9,H42,Q13.81,Q15.0
CPT: 65820-65855,66150,66155,66170,66172,66179-66250,66700-66711,66740,66762,66920-66984,67036,67255, 67500,76514,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,96150-96155, 98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **140**
Condition: MYASTHENIA GRAVIS (See Guideline Notes 61,64,65)
Treatment: MEDICAL THERAPY, THYMECTOMY
ICD-10: G70.00-G70.9,G73.1-G73.3
CPT: 32673,36514,36516,60520-60522,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **141**
Condition: SYSTEMIC LUPUS ERYTHEMATOSUS, OTHER DIFFUSE DISEASES OF CONNECTIVE TISSUE (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: M32.0,M32.10-M32.9,M35.1,M35.9
CPT: 36514,36516,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **142**
Condition: CONDITIONS INVOLVING THE TEMPERATURE REGULATION OF NEWBORNS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: P80.0-P80.9,P81.0-P81.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **143**
Condition: PNEUMOTHORAX AND PLEURAL EFFUSION TUBE THORACOSTOMY (See Guideline Notes 64,65)
Treatment: SURGICAL THERAPY, MEDICAL THERAPY
ICD-10: J90,J91.0-J91.8,J93.0,J93.11-J93.9,J94.0,J94.2,J95.811-J95.812,J98.2,S27.0XXA-S27.0XXD,S27.1XXA-S27.1XXD,S27.2XXA-S27.2XXD
CPT: 31634,32110,32124,32200-32220,32310,32550,32552,32554-32562,32650-32653,32655,32664,32665,33015-33050,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **144**
Condition: HYPOTHERMIA (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY, EXTRACORPOREAL CIRCULATION
ICD-10: T68.XXXA-T68.XXXD
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **145**
Condition: ANEMIA OF PREMATURITY OR TRANSIENT NEONATAL NEUTROPENIA (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: P61.2,P61.5,P61.8-P61.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **146**
Condition: ENTERIC INFECTIONS AND OTHER BACTERIAL FOOD POISONING (See Guideline Notes 64,65,165)
Treatment: MEDICAL THERAPY
ICD-10: A00.0-A00.9,A02.0,A02.8-A02.9,A03.0-A03.9,A04.0-A04.6,A04.71-A04.8,A05.0,A05.2-A05.9,A08.0,A08.11-A08.8,A09
CPT: 44705,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0455,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **147**
Condition: GLYCOGENOSIS (See Guideline Notes 64,65,67)
Treatment: MEDICAL THERAPY
ICD-10: E74.00-E74.09
CPT: 93792,93793,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9357

Line: **148**
Condition: ACQUIRED HEMOLYTIC ANEMIAS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: D59.0-D59.9,D62
CPT: 36514,36516,90935,90937,90945,90947,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **149**
Condition: FEEDING AND EATING DISORDERS OF INFANCY OR CHILDHOOD (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F50.82-F50.89,F98.21-F98.3
CPT: 90846,90849,90853,90882,90887,92526,93792,93793,97802-97804,98966-98969,99051,99060,99201-99239,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017,H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005

Line: **150**
Condition: CERVICAL VERTEBRAL DISLOCATIONS/FRACTURES, OPEN OR CLOSED; OTHER VERTEBRAL DISLOCATIONS/FRACTURES, OPEN OR UNSTABLE; SPINAL CORD INJURIES WITH OR WITHOUT EVIDENCE OF VERTEBRAL INJURY (See Guideline Notes 6,64,65,100,136)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: M43.3-M43.4,M43.5X2-M43.5X3,M48.40XA-M48.40XG,M48.41XA-M48.41XG,M48.42XA-M48.42XG,M48.43XA-M48.43XG,M48.50XA-M48.50XG,M48.51XA-M48.51XG,M48.52XA-M48.52XG,M48.53XA-M48.53XG,M80.08XA-M80.08XG,M80.88XA-M80.88XG,M84.58XA,M84.68XA,S12.000A-S12.000G,S12.001A-S12.001G,S12.01XA-S12.01XG,S12.02XA-S12.02XG,S12.030A-S12.030G,S12.031A-S12.031G,S12.040A-S12.040G,S12.041A-S12.041G,S12.090A-S12.090G,S12.091A-S12.091G,S12.100A-S12.100G,S12.101A-S12.101G,S12.110A-S12.110G,S12.111A-S12.111G,S12.112A-S12.112G,S12.120A-S12.120G,S12.121A-S12.121G,S12.130A-S12.130G,S12.131A-S12.131G,S12.14XA-S12.14XG,S12.150A-S12.150G,S12.151A-S12.151G,S12.190A-S12.190G,S12.191A-S12.191G,S12.200A-S12.200G,S12.201A-S12.201G,S12.230A-S12.230G,S12.231A-S12.231G,S12.24XA-S12.24XG,S12.250A-S12.250G,S12.251A-S12.251G,S12.290A-S12.290G,S12.291A-S12.291G,S12.300A-S12.300G,S12.301A-S12.301G,S12.330A-S12.330G,S12.331A-S12.331G,S12.34XA-S12.34XG,S12.350A-S12.350G,S12.351A-S12.351G,S12.390A-S12.390G,S12.391A-S12.391G,S12.400A-S12.400G,S12.401A-S12.401G,S12.430A-S12.430G,S12.431A-S12.431G,S12.44XA-S12.44XG,S12.450A-S12.450G,S12.451A-S12.451G,S12.490A-S12.490G,S12.491A-S12.491G,S12.500A-S12.500G,S12.501A-S12.501G,S12.530A-S12.530G,S12.531A-S12.531G,S12.54XA-S12.54XG,S12.550A-S12.550G,S12.551A-S12.551G,S12.590A-S12.590G,S12.591A-S12.591G,S12.600A-S12.600G,S12.601A-S12.601G,S12.630A-S12.630G,S12.631A-S12.631G,S12.64XA-S12.64XG,S12.650A-S12.650G,S12.651A-S12.651G,S12.690A-S12.690G,S12.691A-S12.691G,S12.9XXA-S12.9XXD,S13.100A-S13.100D,S13.101A-S13.101D,S13.110A-S13.110D,S13.111A-S13.111D,S13.120A-S13.120D,S13.121A-S13.121D,S13.130A-S13.130D,S13.131A-S13.131D,S13.140A-S13.140D,S13.141A-S13.141D,S13.150A-S13.150D,S13.151A-S13.151D,S13.160A-S13.160D,S13.161A-S13.161D,S13.170A-S13.170D,S13.171A-S13.171D,S13.180A-S13.180D,S13.181A-S13.181D,S14.0XXA-S14.0XXD,S14.101A-S14.101D,S14.102A-S14.102D,S14.103A-S14.103D,S14.104A-S14.104D,S14.105A-S14.105D,S14.106A-S14.106D,S14.107A-S14.107D,S14.108A-S14.108D,S14.109A-S14.109D,S14.111A-S14.111D,S14.112A-S14.112D,S14.113A-S14.113D,S14.114A-S14.114D,S14.115A-S14.115D,S14.116A-S14.116D,S14.117A-S14.117D,S14.118A-S14.118D,S14.119A-S14.119D,S14.121A-S14.121D,S14.122A-S14.122D,S14.123A-S14.123D,S14.124A-S14.124D,S14.125A-S14.125D,S14.126A-S14.126D,S14.127A-S14.127D,S14.128A-S14.128D,S14.129A-S14.129D,S14.131A-S14.131D,S14.132A-S14.132D,S14.133A-S14.133D,S14.134A-S14.134D,S14.135A-S14.135D,S14.136A-S14.136D,S14.137A-S14.137D,S14.138A-S14.138D,S14.139A-S14.139D,S14.141A-S14.141D,S14.142A-S14.142D,S14.143A-S14.143D,S14.144A-S14.144D,S14.145A-S14.145D,S14.146A-S14.146D,S14.147A-S14.147D,S14.148A-S14.148D,S14.149A-S14.149D,S14.151A-S14.151D,S14.152A-S14.152D,S14.153A-S14.153D,S14.154A-S14.154D,S14.155A-S14.155D,S14.156A-S14.156D,S14.157A-S14.157D,S14.158A-S14.158D,S14.159A-S14.159D,S22.000B-S22.000G,S22.001B-S22.001G,S22.002B-S22.002G,S22.008B-S22.008G,S22.009B-S22.009G,S22.010B-S22.010G,S22.011B-S22.011G,S22.012B-S22.012G,S22.018B-S22.018G,S22.019B-S22.019G,S22.020B-S22.020G,S22.021B-S22.021G,S22.022B-S22.022G,S22.028B-S22.028G,S22.029B-S22.029G,S22.030B-S22.030G,S22.031B-S22.031G,S22.032B-S22.032G,S22.038B-S22.038G,S22.039B-S22.039G,S22.040B-S22.040G,S22.041B-S22.041G,S22.042B-S22.042G,S22.048B-S22.048G,S22.049B-S22.049G,S22.050B-S22.050G,S22.051B-S22.051G,S22.052B-S22.052G,S22.058B-S22.058G,S22.059B-S22.059G,S22.060B-S22.060G,S22.061B-S22.061G,S22.062B-S22.062G,S22.068B-S22.068G,S22.069B-

S22.069G,S22.070B-S22.070G,S22.071B-S22.071G,S22.072B-S22.072G,S22.078B-S22.078G,S22.079B-S22.079G,S22.080B-S22.080G,S22.081B-S22.081G,S22.082B-S22.082G,S22.088B-S22.088G,S22.089B-S22.089G,S24.0XXA-S24.0XXD,S24.101A-S24.101D,S24.102A-S24.102D,S24.103A-S24.103D,S24.104A-S24.104D,S24.109A-S24.109D,S24.111A-S24.111D,S24.112A-S24.112D,S24.113A-S24.113D,S24.114A-S24.114D,S24.119A-S24.119D,S24.131A-S24.131D,S24.132A-S24.132D,S24.133A-S24.133D,S24.134A-S24.134D,S24.139A-S24.139D,S24.141A-S24.141D,S24.142A-S24.142D,S24.143A-S24.143D,S24.144A-S24.144D,S24.149A-S24.149D,S24.151A-S24.151D,S24.152A-S24.152D,S24.153A-S24.153D,S24.154A-S24.154D,S24.159A-S24.159D,S32.000B-S32.000G,S32.001B-S32.001G,S32.002A-S32.002G,S32.008B-S32.008G,S32.009B-S32.009G,S32.010B-S32.010G,S32.011B-S32.011G,S32.012A-S32.012G,S32.018B-S32.018G,S32.019B-S32.019G,S32.020B-S32.020G,S32.021B-S32.021G,S32.022A-S32.022G,S32.028B-S32.028G,S32.029B-S32.029G,S32.030B-S32.030G,S32.031B-S32.031G,S32.032A-S32.032G,S32.038B-S32.038G,S32.039B-S32.039G,S32.040B-S32.040G,S32.041B-S32.041G,S32.042A-S32.042G,S32.048B-S32.048G,S32.049B-S32.049G,S32.050B-S32.050G,S32.051B-S32.051G,S32.052A-S32.052G,S32.058B-S32.058G,S32.059B-S32.059G,S32.10XB,S32.110B,S32.111B,S32.112B,S32.119B,S32.120B,S32.121B,S32.122B,S32.129B,S32.130B,S32.131B,S32.132B,S32.139B,S32.14XB,S32.15XB,S32.16XB,S32.17XB,S32.19XB,S34.01XA-S34.01XD,S34.02XA-S34.02XD,S34.101A-S34.101D,S34.102A-S34.102D,S34.103A-S34.103D,S34.104A-S34.104D,S34.105A-S34.105D,S34.109A-S34.109D,S34.111A-S34.111D,S34.112A-S34.112D,S34.113A-S34.113D,S34.114A-S34.114D,S34.115A-S34.115D,S34.119A-S34.119D,S34.121A-S34.121D,S34.122A-S34.122D,S34.123A-S34.123D,S34.124A-S34.124D,S34.125A-S34.125D,S34.129A-S34.129D,S34.131A-S34.131D,S34.132A-S34.132D,S34.139A-S34.139D,Z47.2

CPT: 11010-11012,20660,20661,20665,20690-20694,20930-20938,22100-22116,22310-22505,22532-22819,22840-22855,22859,27202-27216,29015,29040,29710,29720,63001-63173,63295,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **151**
Condition: DISORDERS OF MINERAL METABOLISM, OTHER THAN CALCIUM (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: E83.00-E83.10,E83.110-E83.19,E83.30-E83.49,E83.89
CPT: 93792,93793,97802-97804,98966-98969,99051,99060,99070,99078,99184,99195,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9355

Line: **152**
Condition: NON-PULMONARY TUBERCULOSIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A17.83,A17.9,A18.01-A18.89,A19.0-A19.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **153**
Condition: PYOGENIC ARTHRITIS (See Guideline Notes 6,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: A01.04,A02.23,A39.83,M00.00,M00.011-M00.9,M01.X0,M01.X11-M01.X9
CPT: 20600-20611,23040,23044,24000,24006,24101,24102,25040,25101-25109,26070-26080,27030,27310,27610,28022,28024,29819,29821-29823,29825,29843,29848,29861-29863,29871,29894,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **154**
Condition: VASCULAR INSUFFICIENCY OF INTESTINE (See Guideline Notes 64,65)
Treatment: SURGICAL TREATMENT
ICD-10: K55.011-K55.1,K55.8-K55.9,Z46.59
CPT: 34151,34421,34451,44120-44125,44130,44139-44160,44202-44213,44310,44701,49442,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **155**
Condition: HERPES ZOSTER; HERPES SIMPLEX AND WITH NEUROLOGICAL AND OPHTHALMOLOGICAL COMPLICATIONS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: B00.2-B00.4,B00.50-B00.89,B02.0-B02.1,B02.21-B02.9,B10.01-B10.09,G93.7
CPT: 65430,69676,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **156**
Condition: ACROMEGALY AND GIGANTISM (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: E22.0
CPT: 32553,48140,48155,49411,60200-60240,60270,60271,60512,60600-60650,61548,62100,79005-79445,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **157**
Condition: CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS (See Guideline Notes 7,11,12,19,23,64,65,148)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C17.0-C17.9,C18.0-C18.9,C19-C20,C21.0-C21.8,C49.A0,C49.A3-C49.A9,C7A.010-C7A.029,D01.0-D01.3,D01.40-D01.49,D37.2-D37.5,D37.8,D61.810,G89.3,K62.82-K62.89,K63.89,Z46.59,Z51.0,Z51.11-Z51.12,Z85.038,Z85.048
CPT: 32553,38747,43245,44120-44125,44139-44160,44187,44188,44204-44227,44300-44346,44379,44381,44384,44391-44402,44404,44405,44620-44626,44701,45110-45113,45119,45123,45126,45136,45171-45190,45303,45308-45320,45327,45333-45335,45338-45347,45381-45389,45395,45397,45402,45505,45550,46604,46900-46924,49203-49205,49411,49442,57156,58150,77014,77261-77295,77300-77370,77385-77387,77401-77417,77424-77432,77469,77470,77761-77763,77770-77790,78811-78816,79005-79445,81275,81288,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

Line: **158**
Condition: NON-HODGKIN'S LYMPHOMAS (See Guideline Notes 7,11,12,19,64,65,115)
Treatment: MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C82.00-C82.99,C83.00-C83.99,C84.00-C84.99,C85.10-C85.99,C86.0-C86.6,C88.4-C88.8,C96.0,C96.20-C96.9,D46.20-D46.C,D46.Z-D46.9,D47.01-D47.1,D47.3,D47.Z1-D47.Z9,D61.810,G89.3,Z51.0,Z51.12
CPT: 32553,36522,38100,38120,38542,38720,49411,77014,77261-77295,77300-77307,77321-77370,77385-77387,77401-77431,77469,77470,78811-78816,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9355,S9537

Line: **159**
Condition: TOXIC EPIDERMAL NECROLYSIS AND STAPHYLOCOCCAL SCALDED SKIN SYNDROME; STEVENS-JOHNSON SYNDROME; ERYTHEMA MULTIFORME MAJOR; ECZEMA HERPETICUM (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: B00.0,L00,L12.30-L12.35,L51.1-L51.3
CPT: 36514,36516,65778-65782,68371,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **160**
Condition: TRAUMATIC AMPUTATION OF ARM(S), HAND(S), THUMB(S), AND FINGER(S) (COMPLETE)(PARTIAL) WITH AND WITHOUT COMPLICATION (See Guideline Notes 6,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: S48.011A-S48.011D,S48.012A-S48.012D,S48.019A-S48.019D,S48.021A-S48.021D,S48.022A-S48.022D,S48.029A-S48.029D,S48.111A-S48.111D,S48.112A-S48.112D,S48.119A-S48.119D,S48.121A-S48.121D,S48.122A-S48.122D,S48.129A-S48.129D,S48.911A-S48.911D,S48.912A-S48.912D,S48.919A-S48.919D,S48.921A-S48.921D,S48.922A-S48.922D,S48.929A-S48.929D,S58.011A-S58.011D,S58.012A-S58.012D,S58.019A-S58.019D,S58.021A-S58.021D,S58.022A-S58.022D,S58.029A-S58.029D,S58.111A-S58.111D,S58.112A-S58.112D,S58.119A-S58.119D,S58.121A-S58.121D,S58.122A-S58.122D,S58.129A-S58.129D,S58.911A-S58.911D,S58.912A-S58.912D,S58.919A-S58.919D,S58.921A-S58.921D,S58.922A-S58.922D,S58.929A-S58.929D,S68.011A-S68.011D,S68.012A-S68.012D,S68.019A-S68.019D,S68.021A-S68.021D,

S68.022A-S68.022D,S68.029A-S68.029D,S68.110A-S68.110D,S68.111A-S68.111D,S68.112A-S68.112D,S68.113A-S68.113D,S68.114A-S68.114D,S68.115A-S68.115D,S68.116A-S68.116D,S68.117A-S68.117D,S68.118A-S68.118D,S68.119A-S68.119D,S68.120A-S68.120D,S68.121A-S68.121D,S68.122A-S68.122D,S68.123A-S68.123D,S68.124A-S68.124D,S68.125A-S68.125D,S68.126A-S68.126D,S68.127A-S68.127D,S68.128A-S68.128D,S68.129A-S68.129D,S68.411A-S68.411D,S68.412A-S68.412D,S68.419A-S68.419D,S68.421A-S68.421D,S68.422A-S68.422D,S68.429A-S68.429D,S68.511A-S68.511D,S68.512A-S68.512D,S68.519A-S68.519D,S68.521A-S68.521D,S68.522A-S68.522D,S68.529A-S68.529D,S68.610A-S68.610D,S68.611A-S68.611D,S68.612A-S68.612D,S68.613A-S68.613D,S68.614A-S68.614D,S68.615A-S68.615D,S68.616A-S68.616D,S68.617A-S68.617D,S68.618A-S68.618D,S68.619A-S68.619D,S68.620A-S68.620D,S68.621A-S68.621D,S68.622A-S68.622D,S68.623A-S68.623D,S68.624A-S68.624D,S68.625A-S68.625D,S68.626A-S68.626D,S68.627A-S68.627D,S68.628A-S68.628D,S68.629A-S68.629D,S68.711A-S68.711D,S68.712A-S68.712D,S68.719A-S68.719D,S68.721A-S68.721D,S68.722A-S68.722D,S68.729A-S68.729D

CPT: 11000,11001,11010-11047,20802-20838,20910,20912,20972,20973,23900-23921,24900-24940,25900-25909,26350-26356,26410-26418,26551-26556,26910-26952,64831,64832,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **161**
Condition: GRANULOCYTE DISORDERS (See Guideline Notes 7,11,64,65)
Treatment: MEDICAL THERAPY
ICD-10: D70.0-D70.8,D71,D72.0,D72.89,D76.1-D76.3
CPT: 79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9537

Line: **162**
Condition: BILIARY ATRESIA
Treatment: LIVER TRANSPLANT
ICD-10: Q44.2-Q44.3,T86.40-T86.49,Z48.23,Z52.6
CPT: 47133-47147,86825-86835,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **163**
Condition: NON-HODGKIN'S LYMPHOMAS (See Guideline Notes 7,11,12,14,19)
Treatment: BONE MARROW TRANSPLANT
ICD-10: C82.00-C82.99,C83.00-C83.99,C84.00-C84.99,C85.10-C85.99,C86.0-C86.6,C88.4,C96.4,C96.A-C96.9,D61.810,T86.01-T86.09,T86.5,Z48.290,Z52.000-Z52.098,Z52.3
CPT: 36680,38204-38215,38230-38243,78811-78816,86825-86835,90284,93792,93793,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2142,S2150,S9537

Line: **164**
Condition: CARCINOMA IN SITU OF UPPER AIRWAY, INCLUDING ORAL CAVITY (See Guideline Notes 64,65)
Treatment: INCISION/EXCISION, MEDICAL THERAPY
ICD-10: D00.00-D00.08,K13.29
CPT: 40500-40530,40810-40816,40819,40820,41000-41018,41110-41510,41520,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **165**
Condition: PREVENTIVE FOOT CARE IN HIGH RISK PATIENTS
Treatment: MEDICAL AND SURGICAL TREATMENT OF TOENAILS AND HYPERKERATOSES OF FOOT
ICD-10: E08.40-E08.42,E08.51-E08.52,E08.621,E09.40-E09.42,E09.51-E09.52,E09.621,E10.40-E10.42,E10.51-E10.52,E10.621,E11.40-E11.42,E11.49-E11.59,E11.621,E11.628,E13.40-E13.42,E13.44,E13.51-E13.52,E13.621,G60.0-G60.8,G62.1,I70.201-I70.299,Z86.31
CPT: 11719-11732,11750,28011,28100-28108,28120-28124,28200-28210,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0245-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **166**
Condition: ANAL, RECTAL AND COLONIC POLYPS
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: D12.0-D12.9,D3A.020-D3A.029,K51.40,K62.0-K62.1,K63.5,Z86.010
CPT: 44110,44140-44160,44204-44213,44391-44401,44404,44620-44626,45113-45116,45171,45172,45308-45320,45333-45335,45338,45346,45381-45385,45388,46610-46612,46615,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **167**
Condition: GONOCOCCAL AND CHLAMYDIAL INFECTIONS OF THE EYE; NEONATAL CONJUNCTIVITIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A54.30-A54.39,A74.0,P37.5,P39.1
CPT: 92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **168**
Condition: COMPLICATED HERNIAS; UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER; PERSISTENT HYDROCELE (See Guideline Notes 24,63,64,65,149)
Treatment: REPAIR
ICD-10: K40.00-K40.91,K41.00-K41.11,K41.30-K41.41,K42.0-K42.1,K43.0-K43.1,K43.3-K43.4,K43.6-K43.7,K44.0-K44.1,K45.0-K45.1,K46.0-K46.1,N43.0,N43.2-N43.3,P83.5
CPT: 39503-39541,39560,39561,43281-43283,44050,44120,44346,49491-49572,49582,49587,49590,49650-49659,55040-55060,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **169**
Condition: NON-DIABETIC HYPOGLYCEMIC COMA (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: E15
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **170**
Condition: ACUTE MASTOIDITIS (See Guideline Notes 64,65)
Treatment: MASTOIDECTOMY, MEDICAL THERAPY
ICD-10: H70.001-H70.099,H70.201-H70.229,H75.00-H75.03
CPT: 69420,69421,69433,69436,69501-69540,69601-69646,69670,69700,69801,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **171**
Condition: AMEBIASIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A06.0-A06.3,A06.7,A06.81-A06.9,A07.0-A07.1,A07.8,B60.10-B60.11,B60.19-B60.8
CPT: 92002-92014,92018-92060,92081-92136,92225,92226,92230,92235,92242-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **172**
Condition: HYPERTENSIVE HEART AND RENAL DISEASE (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: I13.0,I13.10-I13.2,I15.0-I15.1,N26.2
CPT: 92960-92971,92978-92998,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **173**
Condition: POSTTRAUMATIC STRESS DISORDER (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F43.10-F43.12
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99281-99285,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005

Line: **174**
Condition: GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS (See Guideline Note 19)
Treatment: SINGLE FOCAL SURGERY
ICD-10: G40.001-G40.219,G40.309-G40.319,Z45.42-Z45.49,Z46.2
CPT: 61531-61537,61540-61543,61566,61567,61720,61735,61760,61850-61888,64568-64570,78608,78609,78811,78814,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **175**
Condition: POLYARTERITIS NODOSA AND ALLIED CONDITIONS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: I67.7,M30.0,M30.2,M30.8,M31.1,M31.7,M35.2
CPT: 36514,36516,92002-92014,92235,92242,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **176**
Condition: COMMON VENTRICLE (See Guideline Notes 64,65)
Treatment: TOTAL REPAIR
ICD-10: Q20.4,Q20.8
CPT: 33600,33602,33608,33610,33615,33617,33620-33622,33692,33694,33735-33750,33764-33768,33924,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **177**
Condition: DISORDERS OF AMINO-ACID TRANSPORT AND METABOLISM (NON PKU); HEREDITARY FRUCTOSE INTOLERANCE (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: E70.20-E70.29,E70.320-E70.39,E70.5-E70.9,E71.0,E71.110-E71.2,E72.00,E72.02-E72.52,E72.59-E72.9,E73.0,E74.12-E74.19,E74.4-E74.8
CPT: 93792,93793,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **178**
Condition: INTRACEREBRAL HEMORRHAGE (See Guideline Notes 6,64,65,90)
Treatment: MEDICAL THERAPY
ICD-10: I61.0-I61.9
CPT: 92507,92508,92521-92526,92607-92609,92633,93792,93793,96150-96155,97012,97110-97127,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513-G0515,S9152

Line: **179**
Condition: ACUTE LEUKEMIA, MYELODYSPLASTIC SYNDROME (See Guideline Notes 7,11,12,14)
Treatment: BONE MARROW TRANSPLANT
ICD-10: C88.8,C90.10-C90.12,C91.00-C91.02,C95.00-C95.02,D46.0-D46.1,D46.20-D46.9,D47.1,D47.3,D61.810,Z48.290, Z52.000-Z52.098,Z52.3
CPT: 36680,38204-38215,38230-38243,86828-86835,93792,93793,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, S2142,S2150,S9537

Line: **180**
Condition: URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: N11.1,N13.0-N13.2,N13.30-N13.5,N28.82
CPT: 50070,50075,50100,50220,50382-50389,50395,50400,50405,50432-50435,50544,50553,50572,50575,50576, 50605,50693-50700,50706-50740,50760,50780-50785,50840-50900,50940,50948,50953,50970,50972,51535, 52276,52290,52301,52310,52315,52327-52346,52352-52354,52356,93792,93793,98966-98969,99051,99060, 99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **181**
Condition: CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (E.G., LIGHTNING STRIKE, HEATSTROKE) (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY, BURN TREATMENT
ICD-10: L55.2,T33.011A-T33.011D,T33.012A-T33.012D,T33.019A-T33.019D,T33.02XA-T33.02XD,T33.09XA-T33.09XD, T33.1XXA-T33.1XXD,T33.2XXA-T33.2XXD,T33.3XXA-T33.3XXD,T33.40XA-T33.40XD,T33.41XA-T33.41XD, T33.42XA-T33.42XD,T33.511A-T33.511D,T33.512A-T33.512D,T33.519A-T33.519D,T33.521A-T33.521D, T33.522A-T33.522D,T33.529A-T33.529D,T33.531A-T33.531D,T33.532A-T33.532D,T33.539A-T33.539D, T33.60XA-T33.60XD,T33.61XA-T33.61XD,T33.62XA-T33.62XD,T33.70XA-T33.70XD,T33.71XA-T33.71XD, T33.72XA-T33.72XD,T33.811A-T33.811D,T33.812A-T33.812D,T33.819A-T33.819D,T33.821A-T33.821D, T33.822A-T33.822D,T33.829A-T33.829D,T33.831A-T33.831D,T33.832A-T33.832D,T33.839A-T33.839D, T33.90XA-T33.90XD,T33.99XA-T33.99XD,T34.011A-T34.011D,T34.012A-T34.012D,T34.019A-T34.019D, T34.02XA-T34.02XD,T34.09XA-T34.09XD,T34.1XXA-T34.1XXD,T34.2XXA-T34.2XXD,T34.3XXA-T34.3XXD, T34.40XA-T34.40XD,T34.41XA-T34.41XD,T34.42XA-T34.42XD,T34.511A-T34.511D,T34.512A-T34.512D, T34.519A-T34.519D,T34.521A-T34.521D,T34.522A-T34.522D,T34.529A-T34.529D,T34.531A-T34.531D, T34.532A-T34.532D,T34.539A-T34.539D,T34.60XA-T34.60XD,T34.61XA-T34.61XD,T34.62XA-T34.62XD, T34.70XA-T34.70XD,T34.71XA-T34.71XD,T34.72XA-T34.72XD,T34.811A-T34.811D,T34.812A-T34.812D, T34.819A-T34.819D,T34.821A-T34.821D,T34.822A-T34.822D,T34.829A-T34.829D,T34.831A-T34.831D, T34.832A-T34.832D,T34.839A-T34.839D,T34.90XA-T34.90XD,T34.99XA-T34.99XD,T67.0XXA-T67.0XXD, T67.1XXA-T67.1XXD,T67.2XXA-T67.2XXD,T67.3XXA-T67.3XXD,T67.4XXA-T67.4XXD,T67.5XXA-T67.5XXD, T67.6XXA-T67.6XXD,T67.7XXA-T67.7XXD,T67.8XXA-T67.8XXD,T67.9XXA-T67.9XXD,T69.011A-T69.011D, T69.012A-T69.012D,T69.019A-T69.019D,T69.021A-T69.021D,T69.022A-T69.022D,T69.029A-T69.029D, T69.1XXA-T69.1XXD,T69.8XXA-T69.8XXD,T69.9XXA-T69.9XXD,T70.20XA-T70.20XD,T70.29XA-T70.29XD, T70.4XXA-T70.4XXD,T70.8XXA-T70.8XXD,T71.20XA-T71.20XD,T71.21XA-T71.21XD,T71.221A-T71.221D, T71.222A-T71.222D,T71.223A-T71.223D,T71.224A-T71.224D,T71.231A-T71.231D,T71.232A-T71.232D, T71.233A-T71.233D,T71.234A-T71.234D,T71.29XA-T71.29XD,T71.9XXA,T73.2XXA-T73.2XXD,T73.8XXA-T73.8XXD,T73.9XXA-T73.9XXD,T75.00XA-T75.00XD,T75.01XA-T75.01XD,T75.09XA-T75.09XD,T75.1XXA-T75.1XXD,T75.20XA-T75.20XD,T75.21XA-T75.21XD,T75.22XA-T75.22XD,T75.23XA-T75.23XD,T75.29XA-T75.29XD,T75.4XXA-T75.4XXD,T75.81XA-T75.81XD,T75.82XA-T75.82XD,T75.89XA-T75.89XD,T78.8XXA-T78.8XXD,T88.51XA-T88.51XD
CPT: 11000,11960-11971,15002-15005,15271-15278,16000-16036,93792,93793,98966-98969,99051,99060,99070, 99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498, 99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **182**
Condition: SEPTICEMIA (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A01.00,A01.02,A01.09-A01.4,A02.1,A20.7,A22.7,A26.7,A32.7,A39.1-A39.2,A39.4,A39.89,A40.0-A40.9,A41.01-A41.9,A42.7,A48.3,A54.86,A77.0,A96.0-A96.9,A98.3-A98.8,A99,B33.4,B37.7,P36.0,P36.10-P36.9,P39.2,R65.10-R65.21,R78.81,T81.12XA-T81.12XD
CPT: 33946-33966,33969,33984-33989,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239, 99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 183
Condition: FRACTURE OF PELVIS, OPEN AND CLOSED (See Guideline Notes 6,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: M84.350A-M84.350G,M84.454A-M84.454G,M84.550A-M84.550G,M84.650A-M84.650G,M91.0,M91.80-M91.92, S32.301A-S32.301G,S32.302A-S32.302G,S32.309A-S32.309G,S32.311A-S32.311G,S32.312A-S32.312G, S32.313A-S32.313G,S32.314A-S32.314G,S32.315A-S32.315G,S32.316A-S32.316G,S32.391A-S32.391G, S32.392A-S32.392G,S32.399A-S32.399G,S32.401A-S32.401G,S32.402A-S32.402G,S32.409A-S32.409G, S32.411A-S32.411G,S32.412A-S32.412G,S32.413A-S32.413G,S32.414A-S32.414G,S32.415A-S32.415G, S32.416A-S32.416G,S32.421A-S32.421G,S32.422A-S32.422G,S32.423A-S32.423G,S32.424A-S32.424G, S32.425A-S32.425G,S32.426A-S32.426G,S32.431A-S32.431G,S32.432A-S32.432G,S32.433A-S32.433G, S32.434A-S32.434G,S32.435A-S32.435G,S32.436A-S32.436G,S32.441A-S32.441G,S32.442A-S32.442G, S32.443A-S32.443G,S32.444A-S32.444G,S32.445A-S32.445G,S32.446A-S32.446B,S32.446G,S32.451A-S32.451G,S32.452A-S32.452G,S32.453A-S32.453G,S32.454A-S32.454G,S32.455A-S32.455G,S32.456A-S32.456G,S32.461A-S32.461G,S32.462A-S32.462G,S32.463A-S32.463G,S32.464A-S32.464G,S32.465A-S32.465G,S32.466A-S32.466G,S32.471A-S32.471G,S32.472A-S32.472G,S32.473A-S32.473G,S32.474A-S32.474G,S32.475A-S32.475G,S32.476A-S32.476G,S32.481A-S32.481G,S32.482A-S32.482G,S32.483A-S32.483G,S32.484A-S32.484G,S32.485A-S32.485G,S32.486A-S32.486G,S32.491A-S32.491G,S32.492A-S32.492G,S32.499A-S32.499G,S32.501A-S32.501G,S32.502A-S32.502G,S32.509A-S32.509G,S32.511A-S32.511G,S32.512A-S32.512G,S32.519A-S32.519G,S32.591A-S32.591G,S32.592A-S32.592G,S32.599A-S32.599G,S32.601A-S32.601G,S32.602A-S32.602G,S32.609A-S32.609G,S32.611A-S32.611G,S32.612A-S32.612G,S32.613A-S32.613G,S32.614A-S32.614G,S32.615A-S32.615G,S32.616A-S32.616G,S32.691A-S32.691G,S32.692A-S32.692G,S32.699A-S32.699G,S32.810A-S32.810G,S32.811A-S32.811G,S32.82XA-S32.82XK,S32.89XA-S32.89XG,S32.9XXA-S32.9XXG,S33.4XXA-S33.4XXD,Z47.2
CPT: 11010-11012,20690-20694,27033,27197,27198,27215-27228,27279-27282,29035-29046,29305,29325,29710, 29720,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051, 99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490, 99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0412-G0415,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line: 184
Condition: ACUTE OSTEOMYELITIS (See Guideline Notes 6,64,65,148)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: A01.05,A02.24,B37.89,M86.00,M86.011-M86.29,M86.9
CPT: 20150,20955-20973,21025,21026,21510,22010,22015,23035,23105,23130,23170-23184,23405,23406,23900-23921,23935,24134-24147,24420,24900-24930,25035,25085,25119,25145-25151,25210-25240,25900-25909, 25920-25931,26034,26910-26952,26992,27025,27054,27070,27071,27290,27295,27303,27360,27590-27598, 27607,27705-27709,27880-27889,28005,28120-28124,28800-28825,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513,G0514

Line: 185
Condition: DIVERTICULITIS OF COLON (See Guideline Notes 64,65)
Treatment: COLON RESECTION, MEDICAL THERAPY
ICD-10: K57.10,K57.12-K57.13,K57.30,K57.32-K57.33,K57.50,K57.52-K57.53,K57.90,K57.92-K57.93
CPT: 33238,44005,44139-44147,44160,44188,44204-44208,44213,44227,44320,44391,44404,44620-44626,44701, 45308-45320,45334,45335,45381,45382,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078, 99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 186
Condition: RHEUMATIC MULTIPLE VALVULAR DISEASE (See Guideline Notes 64,65)
Treatment: SURGICAL TREATMENT
ICD-10: I07.0-I07.9,I08.0-I08.9,I09.1,I09.89,Z79.01
CPT: 33361-33496,33530,33620,33621,33768,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798, 98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line: **187**
Condition: CUSHING'S SYNDROME; HYPERALDOSTERONISM, OTHER CORTICOADRENAL OVERACTIVITY, MEDULLOADRENAL HYPERFUNCTION (See Guideline Notes 64,65,93)
Treatment: MEDICAL THERAPY/ADRENALECTOMY
ICD-10: E24.0,E24.2-E24.9,E26.01-E26.9,E27.0,E27.5-E27.8,E30.1-E30.8,E34.2
CPT: 11981-11983,60540,60545,60650,61546,62100,93792,93793,96150-96155,98966-98969,99051,99060,99070, 99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498, 99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, S9560

Line: **188**
Condition: CONGENITAL TRICUSPID ATRESIA AND STENOSIS (See Guideline Notes 64,65)
Treatment: REPAIR
ICD-10: Q22.4,Q22.6-Q22.9
CPT: 33460-33464,33496,33608,33615,33617,33620,33621,33735-33750,33766,33768,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,98966-98969,99051,99060,99070, 99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498, 99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line: **189**
Condition: CHRONIC ISCHEMIC HEART DISEASE (See Guideline Notes 49,64,65,89)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: I20.1-I20.9,I23.6,I25.10,I25.111-I25.6,I25.701-I25.709,I25.711-I25.719,I25.721-I25.729,I25.731-I25.739,I25.751-I25.759,I25.761-I25.769,I25.791-I25.9,I51.0,I51.3,Q27.30,Q27.4,Q28.0-Q28.1,Z45.010-Z45.09,Z79.01
CPT: 33202,33206-33210,33212-33229,33233-33238,33361-33430,33465,33475,33477,33500,33508-33542,33572, 33681,33922,33973,33974,35001,35182,35189,35226,35256,35286,35572,35600,92920-92938,92943,92944, 92960-92998,93279-93284,93286-93289,93292-93296,93355,93724,93745,93792-93798,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449, 99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514,K0606-K0609,S0340-S0342,S2205-S2209

Line: **190**
Condition: NEOPLASMS OF ISLETS OF LANGERHANS (See Guideline Note 65)
Treatment: EXCISION OF TUMOR
ICD-10: C25.4,D13.7
CPT: 43260-43265,43274-43278,47542,48120,48140,49324,49325,49421,49422,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480, 99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **191**
Condition: CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER (See Guideline Notes 3,7,11,12,16,26,64,65,79,88,148)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY, RADIATION THERAPY AND BREAST RECONSTRUCTION
ICD-10: C50.011-C50.929,D05.00-D05.92,D48.60-D48.62,D61.810,G89.3,N65.0-N65.1,Z15.01-Z15.02,Z40.01-Z40.03, Z42.1,Z44.30-Z44.32,Z45.811-Z45.819,Z51.0,Z51.11-Z51.12,Z79.810,Z80.3,Z85.3,Z90.10-Z90.13
CPT: 11970,13100-13102,19110,19120-19126,19296-19298,19301-19318,19328-19369,32553,38740,38745,49411, 58300,58301,58661,58940,77014,77261-77295,77300-77370,77385-77387,77402-77417,77427,77431,77470, 77520-77763,77770-77790,79005-79445,81519,93792,93793,96150-96155,96377,96405,96406,96420-96450, 96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G6001-G6017,S2066-S2068,S9537,S9560

Line: **192**
Condition: HEREDITARY ANGIOEDEMA (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: D81.810,D84.1,T78.3XXA-T78.3XXD
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **193**
Condition: AUTISM SPECTRUM DISORDERS (See Guideline Notes 65,75)
Treatment: MEDICAL THERAPY/BEHAVIORAL MODIFICATION INCLUDING APPLIED BEHAVIOR ANALYSIS
ICD-10: F84.0,F84.3-F84.9
CPT: 0359T-0374T,90785,90832-90840,90846-90849,90882,90887,93792,93793,96118,98966-98969,99051,99060, 99201-99215,99224-99226,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513, G0514,H0004,H0023,H0032,H0034,H0038,H2010,H2014,H2027,H2032,S9484

Line: **194**
Condition: HEREDITARY ANEMIAS, HEMOGLOBINOPATHIES, AND DISORDERS OF THE SPLEEN (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: D47.4,D55.0-D55.9,D56.0-D56.9,D57.00-D57.20,D57.211-D57.819,D58.0-D58.9,D64.4,D64.89,D73.0-D73.2, D73.4-D73.5,D73.81-D73.89,D74.0-D74.9,D75.0-D75.1,D75.81,D77,Q89.01-Q89.09
CPT: 36514,36516,38100-38102,38120,47562,47563,93792,93793,96150-96155,98966-98969,99051,99060,99070, 99078,99184,99195,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, S9355

Line: **195**
Condition: ACUTE PANCREATITIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: B25.2,B26.3,K85.00-K85.92,Z80.41
CPT: 43260-43265,43273-43278,47542,47562-47564,47600-47620,48000-48020,48105,48120,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480, 99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **196**
Condition: SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN (See Guideline Notes 6,64,65,90)
Treatment: BURR HOLES, CRANIECTOMY/CRANIOTOMY
ICD-10: G93.5-G93.6,I60.00-I60.9,I61.0-I61.9,I62.00-I62.9,I67.1,I67.5,Q28.2-Q28.3,S06.1X0A-S06.1X0D,S06.1X1A-S06.1X1D,S06.1X2A-S06.1X2D,S06.1X3A-S06.1X3D,S06.1X4A-S06.1X4D,S06.1X5A-S06.1X5D,S06.1X6A-S06.1X6D,S06.1X9A-S06.1X9D,S06.340A-S06.340D,S06.341A-S06.341D,S06.342A-S06.342D,S06.343A-S06.343D,S06.344A-S06.344D,S06.345A-S06.345D,S06.346A-S06.346D,S06.347A-S06.349D,S06.350A-S06.350D,S06.351A-S06.351D,S06.352A-S06.352D,S06.353A-S06.353D,S06.354A-S06.354D,S06.355A-S06.355D,S06.356A-S06.356D,S06.357A-S06.359D,S06.360A-S06.360D,S06.361A-S06.361D,S06.362A-S06.362D,S06.363A-S06.363D,S06.364A-S06.364D,S06.365A-S06.365D,S06.366A-S06.366D,S06.367A-S06.369D,S06.371A-S06.371D,S06.372A-S06.372D,S06.373A-S06.373D,S06.374A-S06.374D,S06.375A-S06.375D,S06.376A-S06.376D,S06.377A-S06.379D,S06.380A-S06.380D,S06.381A-S06.381D,S06.382A-S06.382D,S06.383A-S06.383D,S06.384A-S06.384D,S06.385A-S06.385D,S06.386A-S06.386D,S06.387A-S06.389D,S06.4X0A-S06.4X0D,S06.4X1A-S06.4X1D,S06.4X2A-S06.4X2D,S06.4X3A-S06.4X3D,S06.4X4A-S06.4X4D,S06.4X5A-S06.4X5D,S06.4X6A-S06.4X6D,S06.4X7A-S06.4X9D,S06.5X0A-S06.5X0D,S06.5X1A-S06.5X1D,S06.5X2A-S06.5X2D,S06.5X3A-S06.5X3D,S06.5X4A-S06.5X4D,S06.5X5A-S06.5X5D,S06.5X6A-S06.5X6D,S06.5X7A,S06.5X9A-S06.5X9D,S06.6X0A-S06.6X0D,S06.6X1A-S06.6X1D,S06.6X2A-S06.6X2D, S06.6X3A-S06.6X3D,S06.6X4A-S06.6X4D,S06.6X5A-S06.6X5D,S06.6X6A-S06.6X6D,S06.6X9A-S06.6X9D
CPT: 31290,31291,61107-61120,61150-61154,61210,61312-61316,61322,61323,61343,61522-61626,61680-61711, 61781-61783,62100,62143,62160,62220,62223,62272,77263-77290,77295,77300,77306,77307,77332-77336, 77370-77372,77385-77387,77402-77412,77432,92507,92508,92521-92526,92607-92609,92633,93792,93793, 96150-96155,97012,97110-97127,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060, 99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513-G0515,G6001-G6017,S9152

Line: **197**
Condition: BURN, PARTIAL THICKNESS WITHOUT VITAL SITE REQUIRING GRAFTING, UP TO 30% OF BODY SURFACE (See Guideline Notes 6,64,65)
Treatment: FREE SKIN GRAFT, MEDICAL THERAPY
ICD-10: L00,T20.25XA-T20.25XD,T20.26XA-T20.26XD,T20.35XA-T20.35XD,T20.36XA-T20.36XD,T20.65XA-T20.65XD, T20.66XA-T20.66XD,T20.75XA-T20.75XD,T20.76XA-T20.76XD,T21.20XA-T21.20XD,T21.21XA-T21.21XD, T21.22XA-T21.22XD,T21.23XA-T21.23XD,T21.24XA-T21.24XD,T21.25XA-T21.25XD,T21.29XA-T21.29XD, T21.30XA-T21.30XD,T21.31XA-T21.31XD,T21.32XA-T21.32XD,T21.33XA-T21.33XD,T21.34XA-T21.34XD, T21.35XA-T21.35XD,T21.39XA-T21.39XD,T21.60XA-T21.60XD,T21.61XA-T21.61XD,T21.62XA-T21.62XD, T21.63XA-T21.63XD,T21.64XA-T21.64XD,T21.65XA-T21.65XD,T21.69XA-T21.69XD,T21.70XA-T21.70XD, T21.71XA-T21.71XD,T21.72XA-T21.72XD,T21.73XA-T21.73XD,T21.74XA-T21.74XD,T21.75XA-T21.75XD,

T21.79XA-T21.79XD,T22.20XA-T22.20XD,T22.211A-T22.211D,T22.212A-T22.212D,T22.219A-T22.219D, T22.221A-T22.221D,T22.222A-T22.222D,T22.229A-T22.229D,T22.231A-T22.231D,T22.232A-T22.232D, T22.239A-T22.239D,T22.241A-T22.241D,T22.242A-T22.242D,T22.249A-T22.249D,T22.251A-T22.251D, T22.252A-T22.252D,T22.259A-T22.259D,T22.261A-T22.261D,T22.262A-T22.262D,T22.269A-T22.269D, T22.291A-T22.291D,T22.292A-T22.292D,T22.299A-T22.299D,T22.30XA-T22.30XD,T22.311A-T22.311D, T22.312A-T22.312D,T22.319A-T22.319D,T22.321A-T22.321D,T22.322A-T22.322D,T22.329A-T22.329D, T22.331A-T22.331D,T22.332A-T22.332D,T22.339A-T22.339D,T22.341A-T22.341D,T22.342A-T22.342D, T22.349A-T22.349D,T22.351A-T22.351D,T22.352A-T22.352D,T22.359A-T22.359D,T22.361A-T22.361D, T22.362A-T22.362D,T22.369A-T22.369D,T22.391A-T22.391D,T22.392A-T22.392D,T22.399A-T22.399D, T22.60XA-T22.60XD,T22.611A-T22.611D,T22.612A-T22.612D,T22.619A-T22.619D,T22.621A-T22.621D, T22.622A-T22.622D,T22.629A-T22.629D,T22.631A-T22.631D,T22.632A-T22.632D,T22.639A-T22.639D, T22.641A-T22.641D,T22.642A-T22.642D,T22.649A-T22.649D,T22.651A-T22.651D,T22.652A-T22.652D, T22.659A-T22.659D,T22.661A-T22.661D,T22.662A-T22.662D,T22.669A-T22.669D,T22.691A-T22.691D, T22.692A-T22.692D,T22.699A-T22.699D,T22.70XA-T22.70XD,T22.711A-T22.711D,T22.712A-T22.712D, T22.719A-T22.719D,T22.721A-T22.721D,T22.722A-T22.722D,T22.729A-T22.729D,T22.731A-T22.731D, T22.732A-T22.732D,T22.739A-T22.739D,T22.741A-T22.741D,T22.742A-T22.742D,T22.749A-T22.749D, T22.751A-T22.751D,T22.752A-T22.752D,T22.759A-T22.759D,T22.761A-T22.761D,T22.762A-T22.762D, T22.769A-T22.769D,T22.791A-T22.791D,T22.792A-T22.792D,T22.799A-T22.799D,T23.201A-T23.201D, T23.202A-T23.202D,T23.209A-T23.209D,T23.211A-T23.211D,T23.212A-T23.212D,T23.219A-T23.219D, T23.221A-T23.221D,T23.222A-T23.222D,T23.229A-T23.229D,T23.231A-T23.231D,T23.232A-T23.232D, T23.239A-T23.239D,T23.241A-T23.241D,T23.242A-T23.242D,T23.249A-T23.249D,T23.261A-T23.261D, T23.262A-T23.262D,T23.269A-T23.269D,T23.271A-T23.271D,T23.272A-T23.272D,T23.279A-T23.279D, T23.291A-T23.291D,T23.292A-T23.292D,T23.299A-T23.299D,T23.301A-T23.301D,T23.302A-T23.302D, T23.309A-T23.309D,T23.311A-T23.311D,T23.312A-T23.312D,T23.319A-T23.319D,T23.321A-T23.321D, T23.322A-T23.322D,T23.329A-T23.329D,T23.331A-T23.331D,T23.332A-T23.332D,T23.339A-T23.339D, T23.341A-T23.341D,T23.342A-T23.342D,T23.349A-T23.349D,T23.361A-T23.361D,T23.362A-T23.362D, T23.369A-T23.369D,T23.371A-T23.371D,T23.372A-T23.372D,T23.379A-T23.379D,T23.391A-T23.391D, T23.392A-T23.392D,T23.399A-T23.399D,T23.601A-T23.601D,T23.602A-T23.602D,T23.609A-T23.609D, T23.611A-T23.611D,T23.612A-T23.612D,T23.619A-T23.619D,T23.621A-T23.621D,T23.622A-T23.622D, T23.629A-T23.629D,T23.631A-T23.631D,T23.632A-T23.632D,T23.639A-T23.639D,T23.641A-T23.641D, T23.642A-T23.642D,T23.649A-T23.649D,T23.661A-T23.661D,T23.662A-T23.662D,T23.669A-T23.669D, T23.671A-T23.671D,T23.672A-T23.672D,T23.679A-T23.679D,T23.691A-T23.691D,T23.692A-T23.692D, T23.699A-T23.699D,T23.701A-T23.701D,T23.702A-T23.702D,T23.709A-T23.709D,T23.711A-T23.711D, T23.712A-T23.712D,T23.719A-T23.719D,T23.721A-T23.721D,T23.722A-T23.722D,T23.729A-T23.729D, T23.731A-T23.731D,T23.732A-T23.732D,T23.739A-T23.739D,T23.741A-T23.741D,T23.742A-T23.742D, T23.749A-T23.749D,T23.761A-T23.761D,T23.762A-T23.762D,T23.769A-T23.769D,T23.771A-T23.771D, T23.772A-T23.772D,T23.779A-T23.779D,T23.791A-T23.791D,T23.792A-T23.792D,T23.799A-T23.799D, T24.201A-T24.201D,T24.202A-T24.202D,T24.209A-T24.209D,T24.211A-T24.211D,T24.212A-T24.212D, T24.219A-T24.219D,T24.221A-T24.221D,T24.222A-T24.222D,T24.229A-T24.229D,T24.231A-T24.231D, T24.232A-T24.232D,T24.239A-T24.239D,T24.291A-T24.291D,T24.292A-T24.292D,T24.299A-T24.299D, T24.301A-T24.301D,T24.302A-T24.302D,T24.309A-T24.309D,T24.311A-T24.311D,T24.312A-T24.312D, T24.319A-T24.319D,T24.321A-T24.321D,T24.322A-T24.322D,T24.329A-T24.329D,T24.331A-T24.331D, T24.332A-T24.332D,T24.339A-T24.339D,T24.391A-T24.391D,T24.392A-T24.392D,T24.399A-T24.399D, T24.601A-T24.601D,T24.602A-T24.602D,T24.609A-T24.609D,T24.611A-T24.611D,T24.612A-T24.612D, T24.619A-T24.619D,T24.621A-T24.621D,T24.622A-T24.622D,T24.629A-T24.629D,T24.631A-T24.631D, T24.632A-T24.632D,T24.639A-T24.639D,T24.691A-T24.691D,T24.692A-T24.692D,T24.699A-T24.699D, T24.701A-T24.701D,T24.702A-T24.702D,T24.709A-T24.709D,T24.711A-T24.711D,T24.712A-T24.712D, T24.719A-T24.719D,T24.721A-T24.721D,T24.722A-T24.722D,T24.729A-T24.729D,T24.731A-T24.731D, T24.732A-T24.732D,T24.739A-T24.739D,T24.791A-T24.791D,T24.792A-T24.792D,T24.799A-T24.799D, T25.211A-T25.211D,T25.212A-T25.212D,T25.219A-T25.219D,T25.231A-T25.231D,T25.232A-T25.232D, T25.239A-T25.239D,T25.291A-T25.291D,T25.292A-T25.292D,T25.299A-T25.299D,T25.311A-T25.311D, T25.312A-T25.312D,T25.319A-T25.319D,T25.331A-T25.331D,T25.332A-T25.332D,T25.339A-T25.339D, T25.391A-T25.391D,T25.392A-T25.392D,T25.399A-T25.399D,T25.611A-T25.611D,T25.612A-T25.612D, T25.619A-T25.619D,T25.631A-T25.631D,T25.632A-T25.632D,T25.639A-T25.639D,T25.691A-T25.691D, T25.692A-T25.692D,T25.699A-T25.699D,T25.711A-T25.711D,T25.712A-T25.712D,T25.719A-T25.719D, T25.731A-T25.731D,T25.732A-T25.732D,T25.739A-T25.739D,T25.791A-T25.791D,T25.792A-T25.792D, T25.799A-T25.799D

CPT: 11000,11042,11045,11960-11971,15002-15005,15271-15278,16000-16036,92507,92508,92521-92524,92607-92609,92633,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9152

Line: **198**
Condition: CONGENITAL LUNG ANOMALIES (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: Q33.0,Q33.2-Q33.4,Q33.6
CPT: 31601,31820,31825,32140,32141,32480-32488,32501,32505-32507,32662,32663,32666-32670,32800,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **199**
Condition: CHRONIC HEPATITIS; VIRAL HEPATITIS (See Guideline Notes 64,65,76)
Treatment: MEDICAL THERAPY
ICD-10: B15.0-B15.9,B16.0-B16.9,B17.0,B17.10-B17.9,B18.0-B18.9,B19.0,B19.10-B19.9,B25.1,K73.0-K73.9,K74.1-K74.2,K75.4,K75.81,K76.0,K76.4
CPT: 91200,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **200**
Condition: CANCER OF SOFT TISSUE (See Guideline Notes 7,11,12,19,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C38.0,C45.2,C47.0,C47.10-C47.9,C49.0,C49.10-C49.9,D48.1-D48.2,D61.810,G89.3,Z51.0,Z51.11-Z51.12
CPT: 20555,21011-21016,21121,21552-21558,21930-21936,22900-22905,23071-23078,24071-24079,25071-25078,26111-26118,27043-27049,27059,27075-27078,27130,27327-27329,27337,27339,27364,27615-27619,27632,27634,28039-28047,32553,33120,33130,49203-49205,49411,64774-64783,69110,69120,69145-69155,77014,77261-77295,77300-77370,77385-77387,77402-77432,77469,77470,77761-77763,77770-77790,78811-78816,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

Line: **201**
Condition: CANCER OF BONES (See Guideline Notes 6,7,11,12,16,19,64,65,100)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C40.00-C40.92,C41.0-C41.9,C79.51-C79.52,D48.0,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.830
CPT: 19260-19272,20930-20938,20955-20973,21025,21026,21034,21044,21045,21081,21610,21620,22532-22819,22853,22854,22859,23140,23200-23330,23470-23474,23900,24150-24155,24363,24370,24371,24498,24900-24931,25110-25119,25210-25240,25320,25335,25337,25391-25393,25441-25447,25450-25492,25505,25810-25931,26910-26952,27025,27054,27065-27067,27075-27078,27130,27187,27290,27334,27335,27365,27465-27468,27495,27590-27598,27635-27647,27656,27745,27880-27889,28800-28825,31200,31201,31225,31600,32553,32900,36680,38720,38724,49411,61500,61583,61601,63081-63103,63276,63295,63620,63621,67412,69970,77014,77261-77295,77300-77307,77321-77370,77385-77387,77401-77431,77469,77470,77520-77525,78811-78816,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: D5934,D5935,D5984,D5992,D5993,D7440,D7441,G0157-G0161,G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

Line: **202**
Condition: CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS (See Guideline Notes 6,64,65,86,90,92,121)
Treatment: CONSULTATION/MEDICATION MANAGEMENT/BEHAVIORAL SUPPORT
ICD-10: E51.2,F01.50-F01.51,F02.80-F02.81,F03.90-F03.91,F04,F06.0-F06.2,F06.30-F06.8,F07.0,F07.81,F10.26-F10.27,F10.96-F10.97,F13.26-F13.27,F13.96-F13.97,F18.17,F18.27,F18.97,F19.16-F19.17,F19.26-F19.27,F19.96-F19.97,G30.0-G30.9,G31.01-G31.2,G31.83
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,96118,97127,97161-97168,98966-98969,99051,99060,99201-99239,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513-G0515,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9484,T1005

Line: **203**
Condition: SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER (See Guideline Notes 27,64,65,118)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: G47.30-G47.31,G47.33-G47.39,G47.411-G47.429,G47.52
CPT: 21193-21235,30117,30140,30520,31600,31601,31610,31820,31825,42140-42160,42820-42836,93792,93793,94660,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **204**
Condition: DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F32.0-F32.1,F32.81-F32.89,F33.8,F34.0,F34.81-F34.89,F39,N94.3
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,97810-97814,98966-98969,99051,99060,99201-99239,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005

Line: **205**
Condition: PNEUMOCOCCAL PNEUMONIA, OTHER BACTERIAL PNEUMONIA, BRONCHOPNEUMONIA (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A01.03,A02.22,A20.2,A21.2,A48.1,A54.84,A70,J13-J14,J15.0-J15.1,J15.20,J15.211-J15.9,J16.0-J16.8,J17,J18.0-J18.1,J18.8-J18.9,J69.0-J69.8
CPT: 31600,31645,31646,93792,93793,94002-94005,94640,94660-94668,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **206**
Condition: SUPERFICIAL ABSCESSES AND CELLULITIS (See Coding Specification Below) (See Guideline Notes 62,64,65,113)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: A46,A48.2,A48.4,B78.1,E83.2,H00.031-H00.039,H60.00-H60.23,I89.1,J34.0,J38.3,J38.7,K12.2,K14.0,K61.0-K61.4,L01.00-L01.1,L02.01-L02.13,L02.211-L02.93,L03.011-L03.91,L05.01-L05.02,L08.0,L08.81-L08.9,L60.0,L98.3,N34.0,N41.2,N41.4-N41.8,N43.1,N48.21-N48.29,N49.1-N49.2,N49.8-N49.9,N61.0-N61.1,N75.1,N76.4
CPT: 10030,10060-10081,10160,11000-11047,11730-11750,11765-11772,19020,20005,20102,21501,21502,22010,22015,23030,23930,25028,26010,26011,26990,27301,27603,28001-28003,29130,30020,31300-31420,31511-31513,31530,31531,31540-31546,31560-31573,31577,31578,31587,31595,31600,31601,31820,31825,40801,41000-41009,41015-41018,41800,42000,45005,45020,46020,46040-46060,46270,53040,53060,53270,54700,55100,55720,55725,56405,56420,56740,60280,67700,69000,92002-92014,93792,93793,96150-96155,96920-96922,97605-97608,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

ICD-10 J38.3 is included on Line 206 for treatment of abscesses and cellulitis of the vocal cords; it is included on Line 557 for treatment of spastic dysphonia.

Line: **207**
Condition: ZOONOTIC BACTERIAL DISEASES (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A20.0-A20.1,A20.8-A20.9,A21.0-A21.1,A21.3-A21.9,A22.0-A22.2,A22.8-A22.9,A23.0-A23.9,A24.0-A24.9,A25.0-A25.9,A26.0,A26.8-A26.9,A27.0,A27.89-A27.9,A28.0-A28.9,A32.0,A32.81,A32.89-A32.9,Z03.810-Z03.818
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **208**
Condition: DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT (See Guideline Notes 6,62,64,65,133)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: S01.00XA-S01.00XD,S01.01XA-S01.01XD,S01.02XA-S01.02XD,S01.03XA-S01.03XD,S01.04XA-S01.04XD,S01.05XA-S01.05XD,S01.111A-S01.111D,S01.112A-S01.112D,S01.119A-S01.119D,S01.121A-S01.121D,S01.122A-S01.122D,S01.129A-S01.129D,S01.131A-S01.131D,S01.132A-S01.132D,S01.139A-S01.139D,S01.141A-S01.141D,S01.142A-S01.142D,S01.149A-S01.149D,S01.151A-S01.151D,S01.152A-S01.152D,S01.159A-S01.159D,S01.20XA-S01.20XD,S01.21XA-S01.21XD,S01.22XA-S01.22XD,S01.23XA-S01.23XD,S01.24XA-S01.24XD,S01.25XA-S01.25XD,S01.301A-S01.301D,S01.302A-S01.302D,S01.309A-S01.309D,S01.311A-S01.311D,S01.312A-S01.312D,S01.319A-S01.319D,S01.321A-S01.321D,S01.322A-S01.322D,S01.329A-S01.329D,S01.331A-S01.331D,S01.332A-S01.332D,S01.339A-S01.339D,S01.341A-S01.341D,S01.342A-S01.342D,S01.349A-S01.349D,S01.351A-S01.351D,S01.352A-S01.352D,S01.359A-S01.359D,S01.401A-S01.401D,S01.402A-S01.402D,S01.409A-S01.409D,S01.411A-S01.411D,S01.412A-S01.412D,S01.419A-S01.419D,S01.421A-S01.421D,S01.422A-S01.422D,S01.429A-S01.429D,S01.431A-S01.431D,S01.432A-S01.432D,S01.439A-S01.439D,S01.441A-S01.441D,S01.442A-S01.442D,S01.449A-S01.449D,S01.451A-S01.451D,S01.452A-S01.452D,S01.459A-S01.459D,S01.511A-S01.511D,S01.521A-S01.521D,S01.522A-S01.522D,S01.531A-S01.531D,S01.541A-S01.541D,S01.542A-S01.542D,S01.551A-S01.551D,S01.80XA-S01.80XD,S01.81XA-S01.81XD,S01.82XA-S01.82XD,S01.83XA-S01.83XD,S01.84XA-S01.84XD,S01.85XA-S01.85XD,S01.90XA-S01.90XD,S01.91XA-S01.91XD,S01.92XA-S01.92XD,S01.93XA-S01.93XD,

S01.94XA-S01.94XD,S01.95XA-S01.95XD,S08.0XXA-S08.0XXD,S08.111A-S08.111D,S08.112A-S08.112D,
S08.119A-S08.119D,S08.121A-S08.121D,S08.122A-S08.122D,S08.129A-S08.129D,S08.811A-S08.811D,
S08.812A-S08.812D,S08.89XA-S08.89XD,S09.12XA-S09.12XD,S09.301A-S09.301D,S09.302A-S09.302D,
S09.309A-S09.309D,S09.311A-S09.311D,S09.312A-S09.312D,S09.313A-S09.313D,S09.319A-S09.319D,
S09.391A-S09.391D,S09.392A-S09.392D,S09.399A-S09.399D,S09.91XA-S09.91XD,S14.3XXA-S14.3XXD,
S14.4XXA-S14.4XXD,S14.5XXA-S14.5XXD,S14.8XXA-S14.8XXD,S14.9XXA-S14.9XXD,S21.001A-S21.001D,
S21.002A-S21.002D,S21.009A-S21.009D,S21.011A-S21.011D,S21.012A-S21.012D,S21.019A-S21.019D,
S21.021A-S21.021D,S21.022A-S21.022D,S21.029A-S21.029D,S21.031A-S21.031D,S21.032A-S21.032D,
S21.039A-S21.039D,S21.041A-S21.041D,S21.042A-S21.042D,S21.049A-S21.049D,S21.051A-S21.051D,
S21.052A-S21.052D,S21.059A-S21.059D,S21.101A-S21.101D,S21.102A-S21.102D,S21.109A-S21.109D,
S21.111A-S21.111D,S21.112A-S21.112D,S21.119A-S21.119D,S21.121A-S21.121D,S21.122A-S21.122D,
S21.129A-S21.129D,S21.131A-S21.131D,S21.132A-S21.132D,S21.139A-S21.139D,S21.141A-S21.141D,
S21.142A-S21.142D,S21.149A-S21.149D,S21.151A-S21.151D,S21.152A-S21.152D,S21.159A-S21.159D,
S21.201A-S21.201D,S21.202A-S21.202D,S21.209A-S21.209D,S21.211A-S21.211D,S21.212A-S21.212D,
S21.219A-S21.219D,S21.221A-S21.221D,S21.222A-S21.222D,S21.229A-S21.229D,S21.231A-S21.231D,
S21.232A-S21.232D,S21.239A-S21.239D,S21.241A-S21.241D,S21.242A-S21.242D,S21.249A-S21.249D,
S21.251A-S21.251D,S21.252A-S21.252D,S21.259A-S21.259D,S21.90XA-S21.90XD,S21.91XA-S21.91XD,
S21.92XA-S21.92XD,S21.93XA-S21.93XD,S21.94XA-S21.94XD,S21.95XA-S21.95XD,S24.3XXA-S24.3XXD,
S24.4XXA-S24.4XXD,S24.8XXA-S24.8XXD,S24.9XXA-S24.9XXD,S28.1XXA-S28.1XXD,S28.211A-S28.211D,
S28.212A-S28.212D,S28.219A-S28.219D,S28.221A-S28.221D,S28.222A-S28.222D,S28.229A-S28.229D,
S29.021A-S29.021D,S29.022A-S29.022D,S29.029A-S29.029D,S31.000A-S31.000D,S31.010A-S31.010D,
S31.020A-S31.020D,S31.030A-S31.030D,S31.040A-S31.040D,S31.050A-S31.050D,S31.100A-S31.100D,
S31.101A-S31.101D,S31.102A-S31.102D,S31.103A-S31.103D,S31.104A-S31.104D,S31.105A-S31.105D,
S31.109A-S31.109D,S31.110A-S31.110D,S31.111A-S31.111D,S31.112A-S31.112D,S31.113A-S31.113D,
S31.114A-S31.114D,S31.115A-S31.115D,S31.119A-S31.119D,S31.120A-S31.120D,S31.121A-S31.121D,
S31.122A-S31.122D,S31.123A-S31.123D,S31.124A-S31.124D,S31.125A-S31.125D,S31.129A-S31.129D,
S31.130A-S31.130D,S31.131A-S31.131D,S31.132A-S31.132D,S31.133A-S31.133D,S31.134A-S31.134D,
S31.135A-S31.135D,S31.139A-S31.139D,S31.140A-S31.140D,S31.141A-S31.141D,S31.142A-S31.142D,
S31.143A-S31.143D,S31.144A-S31.144D,S31.145A-S31.145D,S31.149A-S31.149D,S31.150A-S31.150D,
S31.151A-S31.151D,S31.152A-S31.152D,S31.153A-S31.153D,S31.154A-S31.154D,S31.155A-S31.155D,
S31.159A-S31.159D,S31.20XA-S31.20XD,S31.21XA-S31.21XD,S31.22XA-S31.22XD,S31.23XA-S31.23XD,
S31.24XA-S31.24XD,S31.25XA-S31.25XD,S31.30XA-S31.30XD,S31.31XA-S31.31XD,S31.32XA-S31.32XD,
S31.33XA-S31.33XD,S31.34XA-S31.34XD,S31.35XA-S31.35XD,S31.40XA-S31.40XD,S31.41XA-S31.41XD,
S31.42XA-S31.42XD,S31.43XA-S31.43XD,S31.44XA-S31.44XD,S31.45XA-S31.45XD,S31.501A-S31.501D,
S31.502A-S31.502D,S31.511A-S31.511D,S31.512A-S31.512D,S31.521A-S31.521D,S31.522A-S31.522D,
S31.531A-S31.531D,S31.532A-S31.532D,S31.541A-S31.541D,S31.542A-S31.542D,S31.551A-S31.551D,
S31.552A-S31.552D,S31.801A-S31.801D,S31.802A-S31.802D,S31.803A-S31.803D,S31.804A-S31.804D,
S31.805A-S31.805D,S31.809A-S31.809D,S31.811A-S31.811D,S31.812A-S31.812D,S31.813A-S31.813D,
S31.814A-S31.814D,S31.815A-S31.815D,S31.819A-S31.819D,S31.821A-S31.821D,S31.822A-S31.822D,
S31.823A-S31.823D,S31.824A-S31.824D,S31.825A-S31.825D,S31.829A-S31.829D,S31.831A-S31.831D,
S31.832A-S31.832D,S31.833A-S31.833D,S31.834A-S31.834D,S31.835A-S31.835D,S31.839A-S31.839D,
S34.4XXA-S34.4XXD,S34.5XXA-S34.5XXD,S34.6XXA-S34.6XXD,S34.8XXA-S34.8XXD,S34.9XXA-S34.9XXD,
S38.211A-S38.211D,S38.212A-S38.212D,S38.221A-S38.221D,S38.222A-S38.222D,S38.231A-S38.231D,
S38.232A-S38.232D,S38.3XXA-S38.3XXD,S39.021A-S39.021D,S39.022A-S39.022D,S39.023A-S39.023D,
S41.001A-S41.001D,S41.002A-S41.002D,S41.009A-S41.009D,S41.011A-S41.011D,S41.012A-S41.012D,
S41.019A-S41.019D,S41.021A-S41.021D,S41.022A-S41.022D,S41.029A-S41.029D,S41.031A-S41.031D,
S41.032A-S41.032D,S41.039A-S41.039D,S41.041A-S41.041D,S41.042A-S41.042D,S41.049A-S41.049D,
S41.051A-S41.051D,S41.052A-S41.052D,S41.059A-S41.059D,S41.101A-S41.101D,S41.102A-S41.102D,
S41.109A-S41.109D,S41.111A-S41.111D,S41.112A-S41.112D,S41.119A-S41.119D,S41.121A-S41.121D,
S41.122A-S41.122D,S41.129A-S41.129D,S41.131A-S41.131D,S41.132A-S41.132D,S41.139A-S41.139D,
S41.141A-S41.141D,S41.142A-S41.142D,S41.149A-S41.149D,S41.151A-S41.151D,S41.152A-S41.152D,
S41.159A-S41.159D,S44.00XA-S44.00XD,S44.01XA-S44.01XD,S44.02XA-S44.02XD,S44.10XA-S44.10XD,
S44.11XA-S44.11XD,S44.12XA-S44.12XD,S44.20XA-S44.20XD,S44.21XA-S44.21XD,S44.22XA-S44.22XD,
S44.30XA-S44.30XD,S44.31XA-S44.31XD,S44.32XA-S44.32XD,S44.40XA-S44.40XD,S44.41XA-S44.41XD,
S44.42XA-S44.42XD,S44.50XA-S44.50XD,S44.51XA-S44.51XD,S44.52XA-S44.52XD,S44.8X1A-S44.8X1D,
S44.8X2A-S44.8X2D,S44.8X9A-S44.8X9D,S44.90XA-S44.90XD,S44.91XA-S44.91XD,S44.92XA-S44.92XD,
S45.301A-S45.301D,S45.302A-S45.302D,S45.309A-S45.309D,S45.311A-S45.311D,S45.312A-S45.312D,
S45.319A-S45.319D,S45.391A-S45.391D,S45.392A-S45.392D,S45.399A-S45.399D,S46.021A-S46.021D,
S46.022A-S46.022D,S46.029A-S46.029D,S46.121A-S46.121D,S46.122A-S46.122D,S46.129A-S46.129D,
S46.221A-S46.221D,S46.222A-S46.222D,S46.229A-S46.229D,S46.321A-S46.321D,S46.322A-S46.322D,
S46.329A-S46.329D,S46.821A-S46.821D,S46.822A-S46.822D,S46.829A-S46.829D,S46.921A-S46.921D,
S46.922A-S46.922D,S46.929A-S46.929D,S51.001A-S51.001D,S51.002A-S51.002D,S51.009A-S51.009D,
S51.011A-S51.011D,S51.012A-S51.012D,S51.019A-S51.019D,S51.021A-S51.021D,S51.022A-S51.022D,
S51.029A-S51.029D,S51.031A-S51.031D,S51.032A-S51.032D,S51.039A-S51.039D,S51.041A-S51.041D,
S51.042A-S51.042D,S51.049A-S51.049D,S51.051A-S51.051D,S51.052A-S51.052D,S51.059A-S51.059D,
S51.801A-S51.801D,S51.802A-S51.802D,S51.809A-S51.809D,S51.811A-S51.811D,S51.812A-S51.812D,
S51.819A-S51.819D,S51.821A-S51.821D,S51.822A-S51.822D,S51.829A-S51.829D,S51.831A-S51.831D,
S51.832A-S51.832D,S51.839A-S51.839D,S51.841A-S51.841D,S51.842A-S51.842D,S51.849A-S51.849D,
S51.851A-S51.851D,S51.852A-S51.852D,S51.859A-S51.859D,S54.00XA-S54.00XD,S54.01XA-S54.01XD,
S54.02XA-S54.02XD,S54.10XA-S54.10XD,S54.11XA-S54.11XD,S54.12XA-S54.12XD,S54.20XA-S54.20XD,
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S54.8X1A-S54.8X1D,S54.8X2A-S54.8X2D,S54.8X9A-S54.8X9D,S54.90XA-S54.90XD,S54.91XA-S54.91XD,

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CPT: 10120,10121,11000-11047,11730,11732,11750,11760,12001-13160,15002-15005,15845,20101-20150,20525, 23040,23044,23397,24000,24006,24101,24102,24341,25101-25109,25260-25272,25295-25310,25320,25335, 25337,25390-25393,25441-25447,25450-25492,25810-25830,25922,26080,26350-26420,26428-26510,26540, 26591,26951,26990,27310,27372,27603,27830,27831,28022,28024,28140,28200,28208,28810-28825,29075, 29130,29515,29580,30901-30906,32653,40650-40654,40830,40831,41250-41252,42180,42182,49904,54437-54440,54520,54660,54670,56800,57200,57210,57287,64702-64714,64718-64721,64727-64792,64820,64831-64862,64872-64911,67930,67935,67950,90675,90676,92002-92014,93792,93793,97110,97112,97140-97168, 97530,97535,97605-97608,97760,97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: D7912,D7920,G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line: **209**
Condition: CANCER OF UTERUS (See Guideline Notes 7,11,12,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C54.0-C54.9,C55,D07.0,D61.810,G89.3,N85.00,N85.02,Z51.0,Z51.11-Z51.12,Z85.42
CPT: 32553,38562,38564,38571-38573,38770,38780,49203-49205,49327,49411,49412,55920,57155,57156,58120, 58150-58294,58346,58541-58544,58548-58554,58570-58575,58953-58956,77014,77261-77295,77300-77370, 77385-77387,77402-77417,77424-77427,77469,77470,77761-77763,77770-77790,93792,93793,96150-96155, 96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G6001-G6017

Line: **210**
Condition: RUPTURE OF LIVER (See Guideline Notes 64,65)
Treatment: SUTURE/REPAIR
ICD-10: K76.3,K76.5,K77,S36.116A-S36.116D
CPT: 47350-47362,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **211**
Condition: CANCER OF THYROID (See Guideline Notes 7,11,12,19,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C73,D44.0,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.850
CPT: 32553,32674,38700-38724,38746,49411,60200-60271,60512,77014,77261-77295,77300-77307,77321-77370, 77385-77387,77401-77427,77469,78811-78816,79005-79445,93792,93793,96150-96155,96377,96405,96406, 96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: D5984,G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513,G0514,G6001-G6017,S9537

Line: **212**
Condition: NON-SUBSTANCE-RELATED ADDICTIVE BEHAVIORAL DISORDERS (See Guideline Notes 64,65) (Note: This line is not priced as part of the list as funding comes from non-OHP sources)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F63.0
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224, 99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004, H0017,H0019,H0023,H0032-H0034,H0036-H0039,H0045,H2010,H2013,H2014,H2021-H2023,H2027,H2032, S5151,S9125,S9484,T1005

Line: **213**
Condition: BULLOUS DERMATOSES OF THE SKIN (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: L10.0-L10.5,L10.81-L10.9,L12.0-L12.2,L12.8-L12.9,L13.0-L13.9,L14
CPT: 36514,36516,65778-65782,68371,77014,93792,93793,96900,96902,96910-96913,98966-98969,99051,99060, 99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **214**
Condition: ACUTE PULMONARY HEART DISEASE AND PULMONARY EMBOLI (See Guideline Notes 64,65,147)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: I26.01-I26.99,I27.82,T79.1XXA-T79.1XXD
CPT: 33910-33916,37191-37193,92960-92971,92978-92998,93792-93798,98966-98969,99051,99060,99070,99078, 99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line: **215**
Condition: CANCER OF KIDNEY AND OTHER URINARY ORGANS (See Guideline Notes 7,11,12,64,65,96)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C64.1-C64.9,C65.1-C65.9,C68.0-C68.8,C7A.093,C79.00-C79.02,D09.19,D30.00-D30.9,D41.00-D41.3,D41.8,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.50,Z85.528-Z85.59
CPT: 32553,32674,38746,49203-49205,49411,50125,50220-50290,50340,50391,50542,50543,50545,50546,50548,50553,50557,50572,50650,50660,50825-50840,51530,51550-51597,51700,51720,52214-52250,52281,52282,52354,52355,52450,52500,53210-53220,58200,58960,77014,77261-77290,77295,77300,77306,77307,77321-77370,77385-77387,77402-77417,77424-77432,77469,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

Line: **216**
Condition: CANCER OF STOMACH (See Guideline Notes 7,11,12,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C16.0-C16.9,C49.A0,C49.A2,C49.A9,C7A.092,D00.2,D37.1,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.028
CPT: 32553,38747,43122,43245,43248,43249,43266,43611-43635,44110-44130,44186,44310,49327,49411,49412,77014,77261-77295,77300-77307,77321-77370,77385-77387,77402-77417,77424-77432,77469,77470,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

Line: **217**
Condition: PORTAL VEIN THROMBOSIS (See Guideline Notes 64,65,77)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: I81
CPT: 37140,37180,37182,37183,49425-49429,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **218**
Condition: TESTICULAR CANCER (See Guideline Notes 7,11,12,14,30)
Treatment: BONE MARROW RESCUE AND TRANSPLANT
ICD-10: C62.00-C62.92,D61.810,T86.5,Z48.290,Z51.11,Z52.000-Z52.098,Z52.3
CPT: 36680,38204-38215,38230-38243,86825-86835,93792,93793,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2142,S2150,S9537

Line: **219**
Condition: DENTAL CONDITIONS (E.G., PERIODONTAL DISEASE) (See Guideline Note 53)
Treatment: BASIC PERIODONTICS
ICD-10: K05.00-K05.20,K05.211-K05.6,K06.010-K06.1,K06.3
HCPCS: D4210-D4212,D4341,D4342,D4910

Line: **220**
Condition: PULMONARY FIBROSIS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: D86.0,D86.2,J84.01-J84.10,J84.111-J84.9,M30.1,M31.30-M31.31,M31.7,M32.13,M33.01,M33.11,M33.21,M33.91,M34.81,M35.02
CPT: 31600,31601,31820,31825,32997,93792,93793,94002-94005,94640,94660-94668,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **221**
Condition: DYSLIPIDEMIAS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: E78.00-E78.6
CPT: 93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99195,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **222**
Condition: DISORDERS OF FLUID, ELECTROLYTE, AND ACID-BASE BALANCE (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY, DIALYSIS
ICD-10: E72.20,E86.0-E86.9,E87.0-E87.6,E87.70-E87.8,E88.3,R57.1-R57.9,T81.10XA-T81.10XD,T81.19XA-T81.19XD, Z49.01-Z49.32
CPT: 36818-36821,36832,36835,36838,36901-36909,49324-49326,49421,49422,49435,49436,90935-90947,90989-90997,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285, 99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, S9339,S9537

Line: **223**
Condition: OCCUPATIONAL LUNG DISEASES (See Guideline Notes 64,65,156)
Treatment: MEDICAL THERAPY
ICD-10: J60-J61,J62.0-J62.8,J63.0-J63.6,J64-J65,J66.0-J66.8,J67.0-J67.9,J68.0-J68.9,Z51.6
CPT: 31600,86003,86008,86486,93792,93793,94002-94005,94640,94660-94668,95004,95018-95180,96150-96155, 98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0424-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, S9441

Line: **224**
Condition: DISEASES AND DISORDERS OF AORTIC VALVE (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL THERAPY
ICD-10: I06.0-I06.9,I35.0-I35.9,I38-I39,Z79.01
CPT: 33361-33413,33417,33496,33530,33620,33621,37246,37247,75557-75565,75573,92960-92971,92978-92998, 93355,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285, 99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line: **225**
Condition: DISORDERS OF PARATHYROID GLAND; BENIGN NEOPLASM OF PARATHYROID GLAND; DISORDERS OF CALCIUM METABOLISM (See Guideline Notes 64,65,149)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: D35.1,D44.2,E20.0-E20.9,E21.0-E21.5,E83.50-E83.81,E89.2,N25.81
CPT: 49185,60500-60512,93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **226**
Condition: ACUTE INFLAMMATION OF THE HEART DUE TO RHEUMATIC FEVER (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: I01.0-I01.9,I02.0
CPT: 92960-92971,92978-92998,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line: **227**
Condition: RUPTURED VISCUS (See Guideline Notes 64,65)
Treatment: REPAIR
ICD-10: K22.3,K62.7,K63.4,K66.1,K92.89,S27.812A-S27.812D,S27.813A-S27.813D,S27.818A-S27.818D,S27.819A-S27.819D
CPT: 43300-43312,43405,44391,44602-44605,45317,45334,45382,45500,45560,45915,57268,57270,93792,93793, 98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **228**
Condition: INTESTINAL MALABSORPTION (See Coding Specification Below) (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: K86.81,K90.0-K90.3,K90.49-K90.89,K91.2
CPT: 93792,93793,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

ICD-10-CM code K90.89 (Other intestinal malabsorption) is included on this line only for chronic steatorrhea, exudative enteropathy, and protein-losing enteropathy.

Line: **229**
Condition: FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES (See Guideline Notes 64,65)
Treatment: SURGICAL TREATMENT
ICD-10: S02.2XXB-S02.2XXG,S02.30XA-S02.30XG,S02.31XA-S02.31XG,S02.32XA-S02.32XG,S02.400A-S02.400G,S02.401A-S02.401G,S02.402A-S02.402G,S02.40AA-S02.40AG,S02.40BA-S02.40BG,S02.40CA-S02.40CG,S02.40DA-S02.40DG,S02.40EA-S02.40EG,S02.40FA-S02.40FG,S02.411A-S02.411G,S02.412A-S02.412G,S02.413A-S02.413G,S02.42XA-S02.42XG,S02.600A-S02.600G,S02.601A-S02.601G,S02.602A-S02.602G,S02.609A-S02.609G,S02.610A-S02.610G,S02.611A-S02.611G,S02.612A-S02.612G,S02.620A-S02.620G,S02.621A-S02.621G,S02.622A-S02.622G,S02.630A-S02.630G,S02.631A-S02.631G,S02.632A-S02.632G,S02.640A-S02.640G,S02.641A-S02.641G,S02.642A-S02.642G,S02.650A-S02.650G,S02.651A-S02.651G,S02.652A-S02.652G,S02.66XA-S02.66XG,S02.670A-S02.670G,S02.671A-S02.671G,S02.672A-S02.672G,S02.69XA-S02.69XG,S02.80XA-S02.80XG,S02.81XA-S02.81XG,S02.82XA-S02.82XG,S02.92XA-S02.92XG,S04.011A-S04.011D,S04.012A-S04.012D,S04.019A-S04.019D,S04.02XA-S04.02XD,S04.031A-S04.031D,S04.032A-S04.032D,S04.039A-S04.039D,S04.10XA-S04.10XD,S04.11XA-S04.11XD,S04.12XA-S04.12XD,S04.20XA-S04.20XD,S04.21XA-S04.21XD,S04.22XA-S04.22XD,S04.30XA-S04.30XD,S04.31XA-S04.31XD,S04.32XA-S04.32XD,S04.40XA-S04.40XD,S04.41XA-S04.41XD,S04.42XA-S04.42XD,S04.50XA-S04.50XD,S04.51XA-S04.51XD,S04.52XA-S04.52XD,S04.60XA-S04.60XD,S04.61XA-S04.61XD,S04.62XA-S04.62XD,S04.70XA-S04.70XD,S04.71XA-S04.71XD,S04.72XA-S04.72XD,S04.811A-S04.811D,S04.812A-S04.812D,S04.819A-S04.819D,S04.891A-S04.891D,S04.892A-S04.892D,S04.899A-S04.899D,S04.9XXA-S04.9XXD
CPT: 10121,11010-11012,12011-12018,20670,20680,20694,21085,21210,21215,21310-21470,30420,30450,31292-31294,92002-92014,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: D5988,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **230**
Condition: MALIGNANT MELANOMA OF SKIN (See Guideline Notes 7,11,12,19,64,65,148)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C43.0,C43.10-C43.9,D03.0,D03.10-D03.9,D61.810,G89.3,Z51.0,Z51.12,Z85.820
CPT: 11600-11646,12001-12020,12031-13160,14350-15005,21011-21016,21552-21558,21632,21930-21936,22901-22905,23071-23078,24071-24079,25071-25078,26111-26118,27043-27049,27059,27075-27078,27327-27329,27337,27339,27364,27615-27619,27632,27634,28039-28047,32553,32674,38700-38780,49411,77014,77261-77295,77300-77307,77321-77370,77385-77387,77401-77432,77469,77470,78811-78816,81210,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,96904,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0219,G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

Line: **231**
Condition: URINARY FISTULA (See Guideline Notes 64,65)
Treatment: SURGICAL TREATMENT
ICD-10: N32.1-N32.2,N82.0-N82.1
CPT: 44320,45820,50040,50045,50382-50389,50395,50432-50435,50520-50526,50688,50900-50930,50961,50970,50980,51800-51845,51880-51980,52234,53080,53085,53660,53661,57330,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 232
Condition: MYCOBACTERIA, FUNGAL INFECTIONS, TOXOPLASMOSIS, AND OTHER OPPORTUNISTIC INFECTIONS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A31.2-A31.9,A42.0-A42.2,A42.89-A42.9,A43.0-A43.9,B37.1,B37.81-B37.82,B38.0-B38.7,B38.81-B38.9,B39.0-B39.9,B40.0-B40.7,B40.81-B40.9,B41.0-B41.9,B42.0-B42.7,B42.81-B42.9,B43.0-B43.9,B44.0-B44.7,B44.89-B44.9,B45.0-B45.7,B45.9,B46.0-B46.9,B47.0-B47.1,B48.0-B48.8,B49,B58.00-B58.1,B58.3,B58.81-B58.9,B59
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 233
Condition: HYPOPLASTIC LEFT HEART SYNDROME
Treatment: REPAIR
ICD-10: Q23.4,Q25.29,Q25.40-Q25.42,Q25.49
CPT: 33615-33622,33750,33764-33768,33924,33946-33966,33969,33984-33989,75557-75565,75573,93355,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 234
Condition: ADULT RESPIRATORY DISTRESS SYNDROME; ACUTE RESPIRATORY FAILURE; RESPIRATORY CONDITIONS DUE TO PHYSICAL AND CHEMICAL AGENTS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: B97.21,J18.2,J70.0,J70.2,J70.5,J80,J81.0,J95.821-J95.822,J96.00-J96.02,J96.20-J96.92
CPT: 31600,31601,31610,31645,31646,31820,31825,33946-33966,33969,33984-33989,93792,93793,94002-94005,94640,94660-94668,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0424-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 235
Condition: ACUTE LYMPHOCYTIC LEUKEMIAS (ADULT) AND MULTIPLE MYELOMA (See Guideline Notes 7,11,12,64,65)
Treatment: MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C88.2-C88.3,C88.8-C88.9,C90.00-C90.32,C91.00-C91.02,D47.2,D61.810,E85.1-E85.4,E85.81-E85.9,G89.3,Z45.49,Z51.0,Z51.12
CPT: 32553,36514,36516,49411,77014,77261-77295,77300-77307,77321-77370,77385-77387,77401-77431,77469,77470,79005-79445,93792,93793,95990,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

Line: 236
Condition: LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS (See Guideline Notes 62,64,65,81)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: A48.0,E08.52,E09.52,E10.52,E11.52,E13.52,I70.211-I70.269,I70.311-I70.369,I70.411-I70.469,I70.511-I70.569,I70.611-I70.669,I70.711-I70.769,I70.92,I73.01-I73.1,I77.76-I77.77,I96,M60.000-M60.005,M60.011-M60.09,M72.6
CPT: 10030,10060,11000-11057,15002,15003,23900-23921,23930,24900-24940,25028,25900-25931,26025,26030,26910-26952,26990,26991,27025,27290,27295,27301,27305,27590-27598,27603,27880-27889,28001-28003,28008,28150,28800-28825,29893,34101-34203,35081,35256,35302-35321,35351-35372,35500,35510-35671,35682-35686,35701-35761,35860,35875-35881,35903,36002,37184-37186,37220-37235,37246-37249,93792,93793,96150-96155,97605-97608,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 237
Condition: TETANUS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A33,A35
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **238**
Condition: ACUTE PROMYELOCYTIC LEUKEMIA (See Guideline Notes 7,11,12,16)
Treatment: MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY, RADIATION AND RADIONUCLEIDE THERAPY
ICD-10: C92.00-C92.02,C92.40-C92.42,C95.00-C95.02,D61.810,G89.3,Z45.49,Z51.0,Z51.12
CPT: 32553,38100,38120,38760,49411,77014,77261-77290,77295,77300,77306,77307,77321-77370,77385-77387, 77401-77427,77469,77520-77525,81246,93792,93793,95990,96150-96155,96377,96405,96406,96420-96450, 96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G6001-G6017,S9537

Line: **239**
Condition: CANCER OF OVARY (See Guideline Notes 7,11,12,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C56.1-C56.9,C57.00-C57.22,C79.60-C79.62,D39.10-D39.12,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.43
CPT: 32553,38571-38573,38770,44110,44120,44140,49203-49205,49255,49327,49411,49412,49419,49422,57156, 58150,58180-58210,58260,58541-58544,58548-58554,58570-58575,58660-58662,58720,58740,58925-58960, 77014,77261-77290,77295,77300,77306,77307,77321-77370,77385-77387,77401-77417,77424-77427,77469, 77470,77750,77790,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549, 96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G6001-G6017,S9537

Line: **240**
Condition: SHORT BOWEL SYNDROME - AGE 5 OR UNDER
Treatment: INTESTINE AND INTESTINE/LIVER TRANSPLANT
ICD-10: K55.30-K55.33,K91.2,P77.1-P77.9,T86.850-T86.859,Z48.23,Z48.288
CPT: 44132,44135,44715-44721,47133-47147,86825-86835,93792,93793,96150-96155,98966-98969,99051,99060, 99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, S2053

Line: **241**
Condition: CONDITIONS REQUIRING HEART-LUNG AND LUNG TRANSPLANTATION (See Guideline Note 151)
Treatment: HEART-LUNG AND LUNG TRANSPLANT
ICD-10: D86.0,E84.0,E84.8,I27.0,I27.89,J41.8,J43.0-J43.8,J47.0-J47.9,J60-J61,J62.0-J62.8,J63.0-J63.6,J65,J66.0-J66.8, J67.0-J67.9,J70.1,J70.3-J70.4,J84.111-J84.17,J84.81-J84.83,J84.841-J84.89,T27.1XXA-T27.1XXD,T27.5XXA-T27.5XXD,T86.810-T86.818,Z48.21,Z48.24,Z48.280
CPT: 32850-32856,33930-33935,33946-33966,33969,33984-33989,81595,86825-86835,93792,93793,94640,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449, 99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0424-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, S2060,S2061

Line: **242**
Condition: ACUTE AND SUBACUTE NECROSIS OF LIVER; SPECIFIED INBORN ERRORS OF METABOLISM (E.G., MAPLE SYRUP URINE DISEASE, TYROSINEMIA)
Treatment: LIVER TRANSPLANT
ICD-10: D81.810,D84.1,E70.20-E70.29,E70.330-E70.331,E70.5-E70.9,E71.0,E71.110-E71.2,E72.10-E72.29,E72.52-E72.53,E72.8,E74.00-E74.09,E80.5,E83.00-E83.10,E83.110-E83.19,K72.00-K72.01,K73.1-K73.8,K76.2,T86.40-T86.49,Z48.23,Z52.6
CPT: 47133-47147,86825-86835,93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078, 99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **243**
Condition: DERMATOLOGICAL PREMALIGNANT LESIONS AND CARCINOMA IN SITU (See Guideline Notes 64,65)
Treatment: DESTRUCT/EXCISION/MEDICAL THERAPY
ICD-10: D04.0,D04.10-D04.9,E70.30,E70.310-E70.329,E70.338-E70.39,L56.5,N48.0
CPT: 11400-11446,11600-11646,13100-13160,14350,17000-17108,17260-17286,69110,69120,69300,93792,93793, 96567,96573,96574,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **244**
Condition: PRIMARY ANGLE-CLOSURE GLAUCOMA (See Guideline Notes 64,65)
Treatment: MEDICAL, SURGICAL AND LASER TREATMENT
ICD-10: H21.81-H21.89,H40.031-H40.039,H40.061-H40.069,H40.20X0-H40.249
CPT: 65860-65880,66150,66160,66179-66185,66250-66505,66625-66635,66761,66762,66990,76514,92002-92014, 92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078, 99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **245**
Condition: CORNEAL ULCER; SUPERFICIAL INJURY OF EYE AND ADNEXA (See Guideline Notes 64,65)
Treatment: CONJUNCTIVAL FLAP; MEDICAL THERAPY
ICD-10: E50.3,H16.001-H16.079,H16.231-H16.239,S00.251A-S00.251D,S00.252A-S00.252D,S00.259A-S00.259D, S05.00XA-S05.00XD,S05.01XA-S05.01XD,S05.02XA-S05.02XD
CPT: 65275,65430,65600,65778-65782,67505,67515,68200,68360,68371,92002-92014,92018-92060,92081-92136, 92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **246**
Condition: TORSION OF TESTIS (See Guideline Notes 64,65)
Treatment: ORCHIECTOMY, REPAIR
ICD-10: N44.00-N44.04
CPT: 54512-54522,54600-54640,54660,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239, 99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **247**
Condition: LIFE-THREATENING EPISTAXIS (See Guideline Notes 64,65)
Treatment: SEPTOPLASTY/REPAIR/CONTROL HEMORRHAGE
ICD-10: R04.0
CPT: 30520-30560,30620-30930,31238,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239, 99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **248**
Condition: RETAINED INTRAOCULAR FOREIGN BODY, MAGNETIC AND NONMAGNETIC (See Guideline Notes 64,65)
Treatment: FOREIGN BODY REMOVAL
ICD-10: H44.601-H44.799
CPT: 65235-65265,66160,66840-66852,66940,67036,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404, 99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **249**
Condition: METABOLIC BONE DISEASE (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: M81.0-M81.8,M83.0-M83.9,M88.0-M88.1,M88.811-M88.9,M90.611-M90.69
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **250**
Condition: PARKINSON'S DISEASE (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: G20,G21.11-G21.9
CPT: 61781,61782,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **251**
Condition: CHRONIC PANCREATITIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: K86.0-K86.1,K86.89
CPT: 43260-43265,43273-43278,47542,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **252**
Condition: MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES OF CENTRAL NERVOUS SYSTEM (See Guideline Notes 64,65,95)
Treatment: MEDICAL THERAPY
ICD-10: G35,G36.0-G36.9,G37.0-G37.9,Z45.49,Z46.2
CPT: 31600,31610,86711,90284,92081-92083,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **253**
Condition: PSYCHOLOGICAL FACTORS AGGRAVATING PHYSICAL CONDITION (E.G., ASTHMA, CHRONIC GI CONDITIONS, HYPERTENSION) (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F54
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224-99226,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0019,H0023,H0032-H0038,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S9484,T1005

Line: **254**
Condition: ARTERIAL EMBOLISM/THROMBOSIS: ABDOMINAL AORTA, THORACIC AORTA (See Guideline Note 65)
Treatment: SURGICAL TREATMENT
ICD-10: I74.01-I74.19,I74.5-I74.8
CPT: 33320-33335,33916,34001-34101,34201,34203,34839-34848,35081,35331,35363-35390,35535-35540,35560,35623-35638,35646,35647,35654,35681-35683,35691-35695,35741-35800,35875,35876,35901,36825,36830,37184-37186,37211,37213,37214,37236,37237,49324-49326,49421,49422,49435,49436,92960-92971,92978-92998,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **255**
Condition: CHRONIC OSTEOMYELITIS (See Guideline Notes 6,64,65,100)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: M46.20-M46.28,M86.30,M86.311-M86.9
CPT: 11000-11047,20005,20150,20690-20694,20930-20938,20955-20973,21620,21627,22532-22819,22840-22848,22853,22854,22859,23035,23105,23130,23170-23184,23220,23395,23935,24134-24147,24150,24152,24420,24498,25035,25085,25119,25145-25151,25210-25240,25320,25337,26034,26230-26236,26320,26951,26992,27070-27078,27187,27303,27360,27465-27468,27598,27607,27620,27640,27641,27745,27880-27888,28005,28120-28124,28800-28825,29075,29345,63045-63048,63081-63091,93792,93793,96150-96155,97012,97110-97124,97140-97168,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **256**
Condition: MULTIPLE ENDOCRINE NEOPLASIA (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: E07.0,E31.1,E31.20-E31.23,Q92.0-Q92.5,Q92.62-Q92.8,Q93.0-Q93.2,Q95.2-Q95.3
CPT: 60210-60240,60270,60271,60500-60512,60540,60545,60650,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **257**
Condition: DEFORMITIES OF HEAD (See Guideline Notes 6,64,65,169)
Treatment: CRANIOTOMY/CRANIECTOMY
ICD-10: M95.2,Q67.4,Q75.0-Q75.9,Q87.0
CPT: 11971,20660,20661,20665,21076,21077,21110,21120-21123,21137-21180,21182-21206,21210,21256-21275,21282,61312-61330,61340,61345,61550-61559,62115-62148,92507,92508,92521-92526,92607-92609,92633,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: D0364-D0367,D5915,D5919,D5924,D5925,D5928-D5931,D5933,D5992,D5993,D7111-D7240,D7280,D7283,D7940-D7955,D8010-D8693,G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9152

Line: **258**
Condition: DISEASES OF MITRAL, TRICUSPID, AND PULMONARY VALVES (See Guideline Notes 64,65)
Treatment: VALVULOPLASTY, VALVE REPLACEMENT, MEDICAL THERAPY
ICD-10: I01.1,I05.0-I05.9,I08.0,I08.8,I34.0-I34.9,I36.0-I36.9,I37.0-I37.9,I38-I39,I51.1-I51.2,Z79.01
CPT: 33418-33465,33470-33496,33530,33620,33621,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **259**
Condition: CANCER OF PENIS AND OTHER MALE GENITAL ORGANS (See Coding Specification Below) (See Guideline Notes 7,11,12,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C60.0-C60.9,C63.00-C63.9,D07.4,D07.60-D07.69,D40.8,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.45,Z85.48-Z85.49
CPT: 11620-11626,17272-17276,32553,49327,49411,49412,52240,54065,54120-54135,54220,54230,54520-54535,54660,55150-55180,55920,58960,74445,77014,77261-77295,77300-77370,77385-77387,77402-77417,77424-77427,77469,77470,77600-77763,77770-77778,77790,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542-96574,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

CPT 96567, 96573 and 96574 are included on this line only for pairing with ICD-10-CM D07.4.

Line: **260**
Condition: CANCER OF ENDOCRINE SYSTEM, EXCLUDING THYROID; CARCINOID SYNDROME (See Guideline Notes 7,11,12,19,25,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C37,C74.00-C74.92,C75.0-C75.9,C7A.00,C7A.091,C7A.094-C7A.098,C79.70-C79.72,D09.3-D09.8,D44.10-D44.12,D44.5-D44.7,D61.810,E34.0,G89.3,Z51.0,Z51.11-Z51.12
CPT: 32553,32673,38204-38215,38230-38241,49411,60500,60512-60650,62165,64788,77014,77261-77295,77300-77307,77321-77370,77385-77387,77402-77432,77469,77470,78811-78816,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S2150,S9537

Line: **261**
Condition: MULTIPLE MYELOMA (See Guideline Notes 7,11,12,14)
Treatment: BONE MARROW TRANSPLANT
ICD-10: C88.0-C88.3,C88.8-C88.9,C90.00-C90.02,C90.20-C90.32,D47.2,D61.810,E85.1-E85.4,E85.81-E85.9,T86.01-T86.09,T86.5,Z48.290,Z52.000-Z52.098,Z52.3
CPT: 36680,38204-38215,38230-38243,86825-86835,90284,93792,93793,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2142,S2150,S9537

Line: **262**
Condition: CANCER OF RETROPERITONEUM, PERITONEUM, OMENTUM AND MESENTERY (See Guideline Notes 7,11,12,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C45.1,C48.0-C48.8,C49.A9,D48.3-D48.4,D61.810,G89.3,Z51.0,Z51.11-Z51.12
CPT: 32553,39010,44820,44850,49203-49205,49255,49327,49411,49412,77014,77261-77290,77295,77300,77306-77370,77385-77387,77402-77417,77424-77427,77469,77470,77761-77763,77770-77790,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

Line:	**263**
Condition:	CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS (See Coding Specification Below) (See Guideline Notes 7,11,12,19,64,65,142,148,174)
Treatment:	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10:	C33,C34.00-C34.92,C38.1-C38.8,C39.0-C39.9,C45.0,C7A.090,D02.1,D02.20-D02.22,D02.4,D38.1-D38.4, D61.810,G89.3,I87.1,J98.59,Z51.0,Z51.11-Z51.12,Z85.118-Z85.20
CPT:	19260-19272,21552,21610,22900,31592,31600,31601,31630,31631,31636-31646,31770,31775,31785,31786, 31820,31825,32320,32440-32488,32501-32550,32552,32553,32650,32662,32663,32666-32671,32673-32701, 32900-32906,32994,38542,38746,38794,39000-39220,49411,77014,77261-77295,77300-77370,77373-77387, 77401-77470,77761-77763,77770-77790,78811-78816,81235,93792,93793,96150-96155,96377,96405,96406, 96420-96450,96542,96549,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513, G0514,G6001-G6017,S9537

ICD-10-CM code I87.1 is included on this line for superior vena cava syndrome only.

Line:	**264**
Condition:	CONGESTIVE HEART FAILURE, CARDIOMYOPATHY, MALIGNANT ARRHYTHMIAS, AND COMPLEX CONGENITAL HEART DISEASE (See Guideline Notes 18,64,65,70,151)
Treatment:	CARDIAC TRANSPLANT; HEART/KIDNEY TRANSPLANT
ICD-10:	I13.11-I13.2,I25.110,I25.5,I40.0-I40.9,I42.0-I42.8,I47.2,I49.01-I49.02,I50.1,I50.20-I50.43,N18.5-N18.6,Q20.1-Q20.5,Q20.8,Q23.4,T86.21-T86.23,T86.290-T86.298,T86.31-T86.39,Z45.09,Z48.21,Z48.280-Z48.288
CPT:	33620,33621,33940-33966,33969,33975-33993,50300-50370,50547,75557-75565,75573,76776,81595,86825-86835,92960-92971,92978-92998,93750,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078, 99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line:	**265**
Condition:	TRACHOMA (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	A71.0-A71.9,B55.1
CPT:	93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line:	**266**
Condition:	ACUTE, SUBACUTE, CHRONIC AND OTHER TYPES OF IRIDOCYCLITIS (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	A18.54,A50.01,A50.30,A50.39,A51.43,A52.71,B58.00,B58.09,D86.83,H16.241-H16.249,H20.00,H20.011-H20.819,H20.9
CPT:	67515,68200,76514,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480, 99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line:	**267**
Condition:	DENTAL CONDITIONS (TIME SENSITIVE EVENTS) (See Guideline Notes 64,65)
Treatment:	URGENT DENTAL SERVICES
ICD-10:	K00.6,K01.0-K01.1,K03.5,K03.81,K04.01-K04.99,K08.3,M27.2-M27.3,S02.5XXD-S02.5XXG
CPT:	41000,41800,41806,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS:	D2910-D2921,D2940,D2950,D2970,D3120,D3220,D3222-D3240,D3351-D3353,D4920,D5410-D5422,D5850, D5851,D6930,D7111,D8695,D9120,D9951,G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513, G0514

Line:	**268**
Condition:	RICKETTSIAL AND OTHER ARTHROPOD-BORNE DISEASES (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	A44.0-A44.9,A68.0-A68.9,A69.20-A69.29,A75.0-A75.9,A77.1-A77.3,A77.40-A77.9,A78,A79.0-A79.1,A79.81-A79.9,A90-A91,A92.0-A92.2,A92.30-A92.9,A93.0-A93.8,A94,A95.0-A95.9,A98.0-A98.2,B33.1,B55.0,B55.2-B55.9, B60.0
CPT:	93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **269**
Condition: DIABETES INSIPIDUS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: E23.2
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **270**
Condition: ADVANCED DEGENERATIVE DISORDERS AND CONDITIONS OF GLOBE (See Guideline Notes 64,65)
Treatment: ENUCLEATION
ICD-10: H35.60-H35.63,H44.311-H44.399,H44.50,H44.511-H44.539,H44.811-H44.89
CPT: 65091,65093,65105,65125-65175,67218,67560,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **271**
Condition: CANCER OF BLADDER AND URETER (See Guideline Notes 7,11,12,64,65,148)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C66.1-C66.9,C67.0-C67.9,C79.11-C79.19,D09.0,D41.4,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.51
CPT: 32553,38562,38564,38571-38573,38780,49327,49411,49412,50125,50220-50290,50340,50400,50405,50542-50548,50553,50572,50605,50650,50660,50693-50695,50780,50820-50840,50976,51530,51550-51597,51700,51720,52214-52250,52281,52282,52327,52332,52354,52355,52450,52500,53210-53220,55840,55920,57156,58960,77014,77261-77295,77300-77370,77385-77387,77402-77417,77424-77427,77469,77470,77761-77763,77770-77790,79005-79445,88120,88121,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

Line: **272**
Condition: TRAUMATIC AMPUTATION OF FOOT/FEET (COMPLETE)(PARTIAL) WITH AND WITHOUT COMPLICATION (See Guideline Notes 6,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: S98.011A-S98.011D,S98.012A-S98.012D,S98.019A-S98.019D,S98.021A-S98.021D,S98.022A-S98.022D,S98.029A-S98.029D,S98.311A-S98.311D,S98.312A-S98.312D,S98.319A-S98.319D,S98.321A-S98.321D,S98.322A-S98.322D,S98.329A-S98.329D,S98.911A-S98.911D,S98.912A-S98.912D,S98.919A-S98.919D,S98.921A-S98.921D,S98.922A-S98.922D,S98.929A-S98.929D
CPT: 11010-11012,20838,27888,28800-28810,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **273**
Condition: LEPROSY, YAWS, PINTA (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A30.0-A30.9,A31.1,A65,A66.0-A66.9,A67.0-A67.9,A69.8-A69.9
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **274**
Condition: RETINOPATHY OF PREMATURITY
Treatment: CRYOSURGERY
ICD-10: H35.101-H35.179,Q82.3
CPT: 67101-67121,67227-67229,92002-92014,92018-92060,92081-92136,92225-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **275**
Condition: UROLOGIC INFECTIONS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A02.25,B37.0,B37.41-B37.49,B37.81,N11.8-N11.9,N12,N13.6,N30.00-N30.01,N30.20-N30.31,N30.80-N30.91, N39.0,N41.0,N45.1-N45.4,N49.0
CPT: 50391,51100,51101,51700,52260,53450,54700,54860,54861,93792,93793,98966-98969,99051,99060,99070, 99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498, 99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **276**
Condition: CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA (See Guideline Notes 7,11,12,16,19,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C4A.0,C4A.10-C4A.9,C44.00-C44.09,C44.101-C44.99,C46.0-C46.4,C46.50-C46.9,C79.2,D48.5,D61.810,G89.3, Z51.0,Z51.11-Z51.12,Z85.828
CPT: 11000-11047,11400-11446,11600-11646,12001-12020,12031-13160,14350-15005,17000-17108,17260-17315, 21011-21014,21016,21230,21235,21552-21558,21930-21936,22901-22905,23071-23078,24071-24079,25071-25078,26111-26118,27043-27048,27059,27327-27329,27337,27339,27364,27615-27619,27632,27634,28039-28047,32553,38542,38700-38745,38760,38765,40530-40654,49411,67840,67917,67950-67975,69110,69120, 69145,69910,77014,77261-77295,77300-77307,77321-77370,77385-77387,77401-77432,77469,77470,77520-77525,78811-78816,79005-79445,92002-92014,92285,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,96904,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513, G0514,G6001-G6017,S9537

Line: **277**
Condition: OTHER PSYCHOTIC DISORDERS (See Guideline Notes 64,65,82)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F22-F24,F28-F29,F53
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511, G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027, H2032,S5151,S9125,S9480,S9484,T1005

Line: **278**
Condition: HYDROPS FETALIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: P56.0,P56.90-P56.99,P83.2
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **279**
Condition: RETINAL DETACHMENT AND OTHER RETINAL DISORDERS (See Guideline Notes 64,65)
Treatment: RETINAL REPAIR, VITRECTOMY
ICD-10: E08.3521-E08.3549,E08.39,E09.3521-E09.3549,E09.39,E10.3521-E10.3549,E10.39,E11.3521-E11.3549,E11.39, E13.3521-E13.3549,E13.39,H31.401-H31.8,H33.001-H33.109,H33.191-H33.23,H33.40-H33.8,H43.00-H43.03, H43.311-H43.319,H44.2C1-H44.2C9,Z51.11
CPT: 66990,67005-67113,67145,67208,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792, 93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449, 99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **280**
Condition: BUDD-CHIARI SYNDROME, AND OTHER VENOUS EMBOLISM AND THROMBOSIS (See Guideline Notes 64,65,77,147)
Treatment: THROMBECTOMY/LIGATION
ICD-10: I82.0-I82.1,I82.210-I82.3,I82.601-I82.709,I82.721-I82.C29,I82.890-I82.91,Z79.01
CPT: 34101,34401,34451-34530,35206-35226,35236-35256,35266-35286,35572,35681,35761-35840,35875,35876, 35905,35907,37140,37160,37182,37183,37187-37193,37212-37214,37238,37239,37248,37249,93792,93793, 98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 281
Condition: LIFE-THREATENING CARDIAC ARRHYTHMIAS (See Guideline Notes 49,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: I46.2-I46.9,I47.0,I47.2,I49.01-I49.02,I49.3,I97.120-I97.121,Z45.010-Z45.09,Z86.74
CPT: 32160,33202-33251,33261-33264,33270-33273,33820,33967,92960-92971,92978-92998,93279-93284,93286-93289,93292-93296,93600-93656,93724,93745,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0448,G0463-G0467,G0490,G0508-G0511,G0513,G0514,K0606-K0609

Line: 282
Condition: ANOREXIA NERVOSA (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F50.00-F50.02
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,97802-97804,98966-98969,99051,99060,99201-99239,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005

Line: 283
Condition: CHRONIC OBSTRUCTIVE PULMONARY DISEASE; CHRONIC RESPIRATORY FAILURE (See Guideline Notes 64,65,112)
Treatment: MEDICAL THERAPY
ICD-10: J41.1,J43.0-J43.9,J44.0-J44.9,J70.8-J70.9,J82,J96.10-J96.12,J98.4
CPT: 31600,32480-32491,32663,32672,93792,93793,94002-94005,94640,94644-94668,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0424-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9346

Line: 284
Condition: DISSECTING OR RUPTURED AORTIC ANEURYSM (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: I71.00-I71.1,I71.3,I71.5,I71.8,I77.72-I77.73
CPT: 32110-32124,32820,33320-33335,33530,33860-33891,33916,34520,34701-34706,34709-34711,34839-34848,35081-35103,35306,35311,35331,35500-35515,35526,35531,35535-35540,35560,35563,35572,35601-35616,35626-35647,35663,35697,35820,35840,35870-35876,35905,35907,36825,36830,37236,37237,75956-75959,92960-92971,92978-92998,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 285
Condition: COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT (See Guideline Notes 6,62,64,65,90,105,131,147,164,170)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: C80.2,D64.81,D78.01,D78.11-D78.22,D89.810-D89.813,E36.01-E36.12,G04.01-G04.02,G04.31-G04.39,G89.12-G89.18,G96.0,G97.0,G97.2,G97.31-G97.32,G97.48-G97.82,H44.40,H44.431-H44.439,H59.111-H59.369,H95.21-H95.54,I77.79,I97.410-I97.89,J95.01-J95.72,J95.830-J95.89,J98.51,K68.11,K91.30-K91.32,K91.61-K91.83,K91.840-K91.841,K91.86,K91.870-K91.89,K94.01-K94.02,K94.11-K94.12,K94.21-K94.22,K94.31,K95.01-K95.89,L76.01-L76.22,M96.621-M96.831,M97.01XA-M97.01XD,M97.02XA-M97.02XD,M97.11XA-M97.11XD,M97.12XA-M97.12XD,M97.21XA-M97.21XD,M97.22XA-M97.22XD,M97.31XA-M97.31XD,M97.32XA-M97.32XD,M97.41XA-M97.41XD,M97.42XA-M97.42XD,M97.8XXA-M97.8XXD,M97.9XXA-M97.9XXD,N98.0,N99.0,N99.115,N99.510-N99.821,N99.89,O86.0,O90.0,O90.2,R50.84,T80.0XXA-T80.0XXD,T80.211A-T80.211D,T80.212A-T80.212D,T80.218A-T80.218D,T80.219A-T80.219D,T80.22XA-T80.22XD,T80.29XA-T80.29XD,T80.51XA-T80.51XD,T80.52XA-T80.52XD,T80.59XA-T80.59XD,T80.810A-T80.810D,T80.818A-T80.818D,T80.89XA-T80.89XD,T80.90XA-T80.90XD,T80.910A-T80.910D,T80.911A-T80.911D,T80.919A-T80.919D,T80.92XA-T80.92XD,T81.30XA-T81.30XD,T81.31XA-T81.31XD,T81.32XA-T81.32XD,T81.33XA-T81.33XD,T81.4XXA-T81.4XXD,T81.520A-T81.520D,T81.521A-T81.521D,T81.522A-T81.522D,T81.523A-T81.523D,T81.524A-T81.524D,T81.525A-T81.525D,T81.526A-T81.526D,T81.710A-T81.710D,T81.711A-T81.711D,T81.718A-T81.718D,T81.719A-T81.719D,T81.72XA-T81.72XD,T81.83XA-T81.83XD,T82.01XA-T82.01XD,T82.02XA-T82.02XD,T82.03XA-T82.03XD,T82.09XA-T82.09XD,T82.110A-T82.110D,T82.111A-T82.111D,T82.118A-T82.118D,T82.119A-T82.119D,T82.120A-T82.120D,T82.121A-T82.121D,T82.128A-T82.128D,T82.129A-T82.129D,T82.190A-T82.190D,T82.191A-T82.191D,T82.198A-T82.198D,T82.199A-T82.199D,T82.211A-T82.211D,T82.212A-T82.212D,T82.213A-T82.213D,T82.218A-T82.218D,T82.221A-T82.221D,T82.222A-T82.222D,T82.223A-T82.223D,T82.228A-T82.228D,T82.310A-T82.310D,T82.311A-T82.311D,T82.312A-T82.312D,T82.318A-T82.318D,T82.319A-T82.319D,T82.320A-T82.320D,T82.321A-T82.321D,T82.322A-T82.322D,

T82.328A-T82.328D,T82.329A-T82.329D,T82.330A-T82.330D,T82.331A-T82.331D,T82.332A-T82.332D, T82.338A-T82.338D,T82.339A-T82.339D,T82.390A-T82.390D,T82.391A-T82.391D,T82.392A-T82.392D, T82.398A-T82.398D,T82.399A-T82.399D,T82.41XA-T82.41XD,T82.42XA-T82.42XD,T82.43XA-T82.43XD, T82.49XA-T82.49XD,T82.510A-T82.510D,T82.511A-T82.511D,T82.512A-T82.512D,T82.513A-T82.513D, T82.514A-T82.514D,T82.515A-T82.515D,T82.518A-T82.518D,T82.519A-T82.519D,T82.520A-T82.520D, T82.521A-T82.521D,T82.522A-T82.522D,T82.523A-T82.523D,T82.524A-T82.524D,T82.525A-T82.525D, T82.528A-T82.528D,T82.529A-T82.529D,T82.530A-T82.530D,T82.531A-T82.531D,T82.532A-T82.532D, T82.533A-T82.533D,T82.534A-T82.534D,T82.535A-T82.535D,T82.538A-T82.538D,T82.539A-T82.539D, T82.590A-T82.590D,T82.591A-T82.591D,T82.592A-T82.592D,T82.593A-T82.593D,T82.594A-T82.594D, T82.595A-T82.595D,T82.598A-T82.598D,T82.599A-T82.599D,T82.6XXA-T82.6XXD,T82.7XXA-T82.7XXD, T82.817A-T82.817D,T82.818A-T82.818D,T82.827A-T82.827D,T82.828A-T82.828D,T82.837A-T82.837D, T82.838A-T82.838D,T82.847A-T82.847D,T82.848A-T82.848D,T82.855A-T82.855D,T82.856A-T82.856D, T82.857A-T82.857D,T82.858A-T82.858D,T82.867A-T82.867D,T82.868A-T82.868D,T82.897A-T82.897D, T82.898A-T82.898D,T82.9XXA-T82.9XXD,T83.010A-T83.010D,T83.011A-T83.011D,T83.012A-T83.012D, T83.020A-T83.020D,T83.022A-T83.022D,T83.030A-T83.030D,T83.032A-T83.032D,T83.090A-T83.090D, T83.092A-T83.092D,T83.110A-T83.110D,T83.111A-T83.111D,T83.112A-T83.112D,T83.113A-T83.113D, T83.118A-T83.118D,T83.120A-T83.120D,T83.121A-T83.121D,T83.122A-T83.122D,T83.123A-T83.123D, T83.128A-T83.128D,T83.190A-T83.190D,T83.191A-T83.191D,T83.192A-T83.192D,T83.193A-T83.193D, T83.198A-T83.198D,T83.21XA-T83.21XD,T83.22XA-T83.22XD,T83.23XA-T83.23XD,T83.24XA-T83.24XD, T83.25XA-T83.25XD,T83.29XA-T83.29XD,T83.410A-T83.410D,T83.418A-T83.418D,T83.420A-T83.420D, T83.428A-T83.428D,T83.490A-T83.490D,T83.498A-T83.498D,T83.510A-T83.510D,T83.511A-T83.511D, T83.512A-T83.512D,T83.518A-T83.518D,T83.590A-T83.590D,T83.591A-T83.591D,T83.592A-T83.592D, 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CPT: 10030,10060,10061,10121-10180,11008,11042-11047,11982,12020,12021,13160,15002-15005,19328,20600-20611,20650,20670,20680,20693,20694,20975,21120,21501,21627,21750,22010,22015,22849-22852,22855,23334,23335,23472-23474,23800,23802,24160,24164,24430,24435,24800,24802,24925-24935,25109,25250,25251,25415,25420,25431-25446,25449,25907-26035,26060-26110,26115-26117,26121-26340,26350-26420,26428-26556,26565,26568-26910,26991,27030,27090,27091,27125-27138,27236,27265,27266,27284,27286,27301,27303,27310,27331,27448,27486-27488,27556,27580-27596,27703,27704,27786,27870,27882-27886,28715,29819,31290,31291,31613,31614,31750-31781,31800-31830,32120,33206-33215,33217-33223,33226-33249,33262-33264,33270-33273,33284,33361-33496,33510-33536,33768,33863,33968,33971,33974,33977,33978,33980-33983,34001-34203,34830,35188-35190,35301-35390,35500-35571,35583-35587,35601-35671,35700,35800-35907,36261,36514,36516,36818-36821,36825-36909,37182-37185,37192,37193,37197,37211,37212,37220-37239,37244-37249,37607,39000,39010,42960-42962,43255,43260-43265,43273-43278,43772-43774,43848,43860,43870,44120,44137,44312,44314,44340,44345,44640,45382,47542,47802,49020,49324,49325,49402-49407,49422,49423,50065,50135,50225,50370,50400,50405,50435,50525,50544,50727,50728,50830,50920-50940,51705,51710,51860-51925,52001,52310,54340-54352,54390,54406,54415,57287,57296,58301,61070,61880-61888,62160,62194,62225,62230,62256,62258,62272,62355,62365,63661-63664,63688,63707,63709,63744,63746,64569,64570,64585,64595,65150-65175,65710-65757,65920,67005-67028,67036-67043,75984,76514,92002-92014,92507,92508,92521-92526,92607-92609,92633,92928-92933,92937,92938,92943,92944,92978,92979,93590-93592,93644,93792,93793,97012,97110-97127,97140-97168,97530,97535,97542,97605-97608,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0448,G0463-G0467,G0490,G0508-G0511,G0513-G0515,S9152

Line: **286**
Condition: CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS (See Guideline Notes 7,11,12,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C51.0-C51.9,C52,C57.00-C57.9,D07.1-D07.2,D07.30-D07.39,D39.2-D39.9,D61.810,G89.3,R87.620-R87.629,Z51.0,Z51.11-Z51.12
CPT: 11620-11626,32553,38562,38564,38571-38573,38760,49327,49411,49412,55920,56501,56515,56620-56640,57065,57106-57112,57156,57420,57421,57520,57530,57550,58150,58180-58260,58275,58285,58290,58541-58544,58548-58554,58570-58575,58661,58943-58960,77014,77261-77290,77295,77300-77370,77385-77387,77401-77417,77424-77427,77469,77470,77750-77763,77770-77790,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

Line: **287**
Condition: CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX (See Coding Specification Below) (See Guideline Notes 6,7,11,12,16,19,35,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C00.0-C00.9,C01,C02.0-C02.9,C03.0-C03.9,C04.0-C04.9,C05.0-C05.9,C06.0-C06.2,C06.80-C06.9,C07,C08.0-C08.9,C09.0-C09.9,C10.0-C10.9,C11.0-C11.9,C12,C13.0-C13.9,C14.0-C14.8,C30.0-C30.1,C31.0-C31.9,C32.0-C32.9,C76.0,D02.0,D02.3,D11.0,D37.01-D37.02,D37.030-D37.09,D38.0,D38.5-D38.6,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.21-Z85.22,Z85.810-Z85.819
CPT: 13132,13151,20962,21011-21014,21016,21552-21558,30117,30118,30520,31075-31230,31237,31300-31370,31380-31395,31540,31541,31572,31600,31601,31611,31820,31825,32553,38700-38724,40500-40530,40810-40816,40819,40845,41019,41110-41155,41820,41825-41827,41850,42104-42120,42280,42281,42410-42500,42826,42842-42845,42890-42950,43450,43496,49411,60220,69110,69150,69155,69502,77014,77261-77295,77300-77370,77385-77387,77401-77432,77469,77470,77520-77525,77750-77763,77770-77790,78811-78816,79005-79445,92507,92508,92521-92526,92607-92609,92633,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: D5983-D5985,D7440,D7441,D7920,D7981,G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9152,S9537

ICD-10-CM code D11.0 is included on this line only for parotid gland pleomorphic adenomas.

Line: **288**
Condition: OSTEOPETROSIS (See Guideline Notes 7,11,14)
Treatment: BONE MARROW RESCUE AND TRANSPLANT
ICD-10: D61.810,Q78.2,T86.01-T86.09,T86.5,Z48.290,Z52.000-Z52.098,Z52.3
CPT: 36680,38204-38215,38230-38243,86825-86835,93792,93793,96150-96155,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2142,S2150,S9537

Line: **289**
Condition: CRUSH AND OTHER INJURIES OF DIGITS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: S65.401A-S65.401D,S65.402A-S65.402D,S65.409A-S65.409D,S65.411A-S65.411D,S65.412A-S65.412D,S65.419A-S65.419D,S65.491A-S65.491D,S65.492A-S65.492D,S65.499A-S65.499D,S65.500A-S65.500D,S65.501A-S65.501D,S65.502A-S65.502D,S65.503A-S65.503D,S65.504A-S65.504D,S65.505A-S65.505D,S65.506A-S65.506D,S65.507A-S65.507D,S65.508A-S65.508D,S65.509A-S65.509D,S65.510A-S65.510D,S65.511A-S65.511D,S65.512A-S65.512D,S65.513A-S65.513D,S65.514A-S65.514D,S65.515A-S65.515D,S65.516A-S65.516D,S65.517A-S65.517D,S65.518A-S65.518D,S65.519A-S65.519D,S65.590A-S65.590D,S65.591A-S65.591D,S65.592A-S65.592D,S65.593A-S65.593D,S65.594A-S65.594D,S65.595A-S65.595D,S65.596A-S65.596D,S65.597A-S65.597D,S65.598A-S65.598D,S65.599A-S65.599D,S67.00XA-S67.00XD,S67.01XA-S67.01XD,S67.02XA-S67.02XD,S67.10XA-S67.10XD,S67.190A-S67.190D,S67.191A-S67.191D,S67.192A-S67.192D,S67.193A-S67.193D,S67.194A-S67.194D,S67.195A-S67.195D,S67.196A-S67.196D,S67.197A-S67.197D,S67.198A-S67.198D,S97.101A-S97.101D,S97.102A-S97.102D,S97.109A-S97.109D,S97.111A-S97.111D,S97.112A-S97.112D,S97.119A-S97.119D,S97.121A-S97.121D,S97.122A-S97.122D,S97.129A-S97.129D
CPT: 11730,11740,11760,20973,25300,25301,29130,35207,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **290**
Condition: ACUTE STRESS DISORDER (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F43.0,R45.7
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99224,99231-99239,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0023,H0032-H0038,H0045,H2010,H2012,H2013,H2021-H2023,H2027,H2032,H2033,S5151,S9125,S9484,T1005

Line: **291**
Condition: ADRENAL OR CUTANEOUS HEMORRHAGE OF FETUS OR NEONATE (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: P54.0,P54.4-P54.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **292**
Condition: NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS (See Coding Specification Below) (See Guideline Notes 6,64,65,170)
Treatment: MEDICAL AND SURGICAL TREATMENT (E.G., DURABLE MEDICAL EQUIPMENT AND ORTHOPEDIC PROCEDURE)
ICD-10: A33,A50.40,A50.43,A50.45,A52.10-A52.19,A52.3,A81.00-A81.83,A87.1-A87.2,A88.8,A89,C70.0-C70.9,C71.0-C71.9,C72.0-C72.1,C72.20-C72.9,D33.9,D81.3,D81.5,E00.0-E00.9,E45,E70.0-E70.1,E70.20-E70.29,E70.330-E70.331,E70.5-E70.9,E71.0,E71.110-E71.548,E72.00,E72.02-E72.51,E72.59-E72.9,E74.00-E74.09,E74.20-E74.29,E75.00-E75.09,E75.11-E75.23,E75.240-E75.6,E76.01-E76.1,E76.210-E76.9,E77.0-E77.9,E78.70-E78.9,E79.1-E79.9,E80.0-E80.1,E80.20-E80.3,E83.00-E83.09,E88.2,E88.40-E88.49,E88.89,F01.50-F01.51,F03.90-F03.91,F06.1,F06.8,F07.89,F71-F79,F84.0-F84.3,F84.8,G04.1,G04.81-G04.91,G10,G11.0-G11.9,G12.0-G12.1,G12.21-G12.9,G13.1-G13.8,G14-G20,G21.0,G21.11-G21.9,G23.0-G23.9,G24.01,G24.1-G24.2,G24.8,G25.4-G25.5,G25.82,G25.9,G30.0-G30.8,G31.01-G31.83,G31.85-G31.9,G32.0,G32.81-G32.89,G35,G36.0-G36.9,G37.0-G37.9,G40.011-G40.019,G40.111-G40.119,G40.211-G40.219,G40.311-G40.319,G40.411-G40.419,G40.811,G40.89,G40.911-G40.919,G60.0-G60.8,G61.0-G61.1,G61.81-G61.89,G62.0-G62.2,G62.81-G62.89,G64,G71.0,G71.11-G71.8,G72.0-G72.3,G72.41-G72.89,G73.7,G80.0-G80.9,G81.00-G81.94,G82.20-G82.54,G83.0,G83.10-G83.9,G90.01-G90.1,G90.3-G90.4,G90.50,G90.511-G90.8,G91.0-G91.9,G92,G93.0-G93.1,G93.40-G93.81,G93.89,G94,G95.0,G95.11-G95.89,G97.0,G97.2,G97.31-G97.32,G97.48-G97.49,G97.61-G97.82,G98.0,G99.0-G99.8,H49.811-H49.819,I61.0-I61.9,I62.00-I62.9,I63.30,I63.311-I63.312,I63.319-I63.322,I63.329-I63.332,I63.339-I63.342,I63.349-I63.412,I63.419-I63.422,I63.429-I63.432,I63.439-I63.442,I63.449-I63.512,I63.519-I63.522,I63.529-I63.532,I63.539-I63.542,I63.549-I63.9,I67.3,I67.81-I67.83,I67.841-I67.89,I69.010-I69.018,I69.031-I69.090,I69.093,I69.110-I69.118,I69.131-I69.190,I69.193,I69.210-I69.218,I69.231-I69.290,I69.293,I69.310-I69.318,I69.331-I69.390,I69.393,I69.810-I69.818,I69.831-I69.890,I69.893,I69.910-I69.918,I69.931-I69.990,I69.993,I97.810-I97.821,M14.60,M14.611-M14.632,M14.641-M14.69,M24.50,M24.511-M24.576,M61.111-M61.112,M61.121-M61.122,M61.131-M61.132,M61.141-M61.142,M61.144-M61.145,M61.151-M61.152,M61.161-M61.162,M61.171-M61.172,M61.174-M61.175,M61.177-M61.178,M61.18-M61.19,M61.211-M61.212,M61.221-M61.222,M61.231-M61.232,M61.241-M61.242,M61.251-M61.252,M61.261-M61.262,M61.271-M61.272,M61.28-M61.29,M61.311-M61.312,M61.321-M61.322,M61.331-M61.332,M61.341-M61.342,M61.351-M61.352,M61.361-M61.362,M61.371-M61.372,M61.38-M61.39,M61.411-M61.412,M61.421-M61.422,M61.431-M61.432,M61.441-M61.442,M61.451-M61.452,M61.461-M61.462,M61.471-M61.472,M61.48-M61.49,M61.511-M61.512,M61.521-M61.522,M61.531-M61.532,M61.541-M61.542,M61.551-M61.552,M61.561-M61.562,M61.571-M61.572,M61.58-

M61.59,M62.3,M62.411-M62.49,M62.511-M62.522,M62.531-M62.532,M62.541-M62.542,M62.551-M62.59, M62.89,M67.00-M67.02,P07.00-P07.39,P10.0-P10.9,P11.0,P11.2,P11.5-P11.9,P19.0-P19.9,P24.00-P24.21, P24.80-P24.9,P35.0-P35.9,P37.0-P37.9,P39.2,P50.0-P50.9,P51.0-P51.9,P52.0-P52.1,P52.21-P52.9,P54.1-P54.9, P55.1-P55.9,P56.0,P56.90-P56.99,P57.0,P91.2,P91.60-P91.63,P96.81,Q00.0-Q00.2,Q01.0-Q01.9,Q02,Q03.0-Q03.9,Q04.0-Q04.9,Q05.0-Q05.9,Q06.0-Q06.9,Q07.00-Q07.9,Q68.1,Q74.3,Q77.3,Q77.6,Q78.0-Q78.3,Q78.5-Q78.6,Q85.1,Q86.0-Q86.8,Q87.1-Q87.3,Q87.40,Q87.410-Q87.89,Q89.4-Q89.8,Q90.0-Q90.9,Q91.0-Q91.7,Q92.0-Q92.5,Q92.62-Q92.9,Q93.0-Q93.7,Q93.81-Q93.9,Q95.2-Q95.8,Q96.0-Q96.9,Q97.0-Q97.8,Q98.0-Q98.3,Q98.5-Q98.8,Q99.0-Q99.8,R41.4,R41.81,R53.2,R54,S06.370A-S06.370D,S06.810A-S06.810D,S06.811A-S06.811D, S06.812A-S06.812D,S06.813A-S06.813D,S06.814A-S06.814D,S06.815A-S06.815D,S06.816A-S06.816D, S06.817A-S06.819D,S06.820A-S06.820D,S06.821A-S06.821D,S06.822A-S06.822D,S06.823A-S06.823D, S06.824A-S06.824D,S06.825A-S06.825D,S06.826A-S06.826D,S06.827A-S06.829D,S06.890A-S06.890D, S06.891A-S06.891D,S06.892A-S06.892D,S06.893A-S06.893D,S06.894A-S06.894D,S06.895A-S06.895D, S06.896A-S06.896D,S06.897A-S06.899D,S06.9X0A-S06.9X0D,S06.9X1A-S06.9X1D,S06.9X2A-S06.9X2D, S06.9X3A-S06.9X3D,S06.9X4A-S06.9X4D,S06.9X5A-S06.9X5D,S06.9X6A-S06.9X6D,S06.9X7A-S06.9X9D, S14.0XXA-S14.0XXD,S14.101A-S14.101D,S14.102A-S14.102D,S14.103A-S14.103D,S14.104A-S14.104D, S14.105A-S14.105D,S14.106A-S14.106D,S14.107A-S14.107D,S14.108A-S14.108D,S14.109A-S14.109D, S14.111A-S14.111D,S14.112A-S14.112D,S14.113A-S14.113D,S14.114A-S14.114D,S14.115A-S14.115D, S14.116A-S14.116D,S14.117A-S14.117D,S14.118A-S14.118D,S14.119A-S14.119D,S14.121A-S14.121D, S14.122A-S14.122D,S14.123A-S14.123D,S14.124A-S14.124D,S14.125A-S14.125D,S14.126A-S14.126D, S14.127A-S14.127D,S14.128A-S14.128D,S14.129A-S14.129D,S14.131A-S14.131D,S14.132A-S14.132D, S14.133A-S14.133D,S14.134A-S14.134D,S14.135A-S14.135D,S14.136A-S14.136D,S14.137A-S14.137D, S14.138A-S14.138D,S14.139A-S14.139D,S14.141A-S14.141D,S14.142A-S14.142D,S14.143A-S14.143D, S14.144A-S14.144D,S14.145A-S14.145D,S14.146A-S14.146D,S14.147A-S14.147D,S14.148A-S14.148D, S14.149A-S14.149D,S14.151A-S14.151D,S14.152A-S14.152D,S14.153A-S14.153D,S14.154A-S14.154D, S14.155A-S14.155D,S14.156A-S14.156D,S14.157A-S14.157D,S14.158A-S14.158D,S14.159A-S14.159D, S14.2XXA-S14.2XXD,S14.3XXA-S14.3XXD,S24.0XXA-S24.0XXD,S24.101A-S24.101D,S24.102A-S24.102D, S24.103A-S24.103D,S24.104A-S24.104D,S24.109A-S24.109D,S24.111A-S24.111D,S24.112A-S24.112D, S24.113A-S24.113D,S24.114A-S24.114D,S24.119A-S24.119D,S24.131A-S24.131D,S24.132A-S24.132D, S24.133A-S24.133D,S24.134A-S24.134D,S24.139A-S24.139D,S24.141A-S24.141D,S24.142A-S24.142D, S24.143A-S24.143D,S24.144A-S24.144D,S24.149A-S24.149D,S24.151A-S24.151D,S24.152A-S24.152D, S24.153A-S24.153D,S24.154A-S24.154D,S24.159A-S24.159D,S24.2XXA-S24.2XXD,S34.01XA-S34.01XD, S34.02XA-S34.02XD,S34.101A-S34.101D,S34.102A-S34.102D,S34.103A-S34.103D,S34.104A-S34.104D, S34.105A-S34.105D,S34.109A-S34.109D,S34.111A-S34.111D,S34.112A-S34.112D,S34.113A-S34.113D, S34.114A-S34.114D,S34.115A-S34.115D,S34.119A-S34.119D,S34.121A-S34.121D,S34.122A-S34.122D, S34.123A-S34.123D,S34.124A-S34.124D,S34.125A-S34.125D,S34.129A-S34.129D,S34.131A-S34.131D, S34.132A-S34.132D,S34.139A-S34.139D,S34.21XA-S34.21XD,S34.22XA-S34.22XD,S34.3XXA-S34.3XXD, S34.4XXA-S34.4XXD,T40.0X1A-T40.0X1D,T40.0X2A-T40.0X2D,T40.0X3A-T40.0X3D,T40.0X4A-T40.0X4D, T40.1X1A-T40.1X1D,T40.1X2A-T40.1X2D,T40.1X3A-T40.1X3D,T40.1X4A-T40.1X4D,T40.2X1A-T40.2X1D, T40.2X2A-T40.2X2D,T40.2X3A-T40.2X3D,T40.2X4A-T40.2X4D,T40.3X1A-T40.3X1D,T40.3X2A-T40.3X2D, T40.3X3A-T40.3X3D,T40.3X4A-T40.3X4D,T40.4X1A-T40.4X1D,T40.4X2A-T40.4X2D,T40.4X3A-T40.4X3D, T40.4X4A-T40.4X4D,T40.5X1A-T40.5X1D,T40.5X2A-T40.5X2D,T40.5X3A-T40.5X3D,T40.5X4A-T40.5X4D, T40.601A-T40.601D,T40.602A-T40.602D,T40.603A-T40.603D,T40.604A-T40.604D,T40.691A-T40.691D, T40.692A-T40.692D,T40.693A-T40.693D,T40.694A-T40.694D,T40.7X1A-T40.7X1D,T40.7X2A-T40.7X2D, T40.7X3A-T40.7X3D,T40.7X4A-T40.7X4D,T40.8X1A-T40.8X1D,T40.8X2A-T40.8X2D,T40.8X3A-T40.8X3D, T40.8X4A-T40.8X4D,T40.901A-T40.901D,T40.902A-T40.902D,T40.903A-T40.903D,T40.904A-T40.904D, T40.991A-T40.991D,T71.111A-T71.111D,T71.112A-T71.112D,T71.113A-T71.113D,T71.114A-T71.114D, T71.121A-T71.121D,T71.122A-T71.122D,T71.123A-T71.123D,T71.124A-T71.124D,T71.131A-T71.131D, T71.132A-T71.132D,T71.133A-T71.133D,T71.134A-T71.134D,T71.141A-T71.141D,T71.143A-T71.143D, T71.144A-T71.144D,T71.151A-T71.151D,T71.152A-T71.152D,T71.153A-T71.153D,T71.154A-T71.154D, T71.161A-T71.161D,T71.162A-T71.162D,T71.163A-T71.163D,T71.164A-T71.164D,T71.191A-T71.191D, T71.192A-T71.192D,T71.193A-T71.193D,T71.194A-T71.194D,T71.20XA-T71.20XD,T71.21XA-T71.21XD, T71.221A-T71.221D,T71.222A-T71.222D,T71.223A-T71.223D,T71.224A-T71.224D,T71.231A-T71.231D, T71.232A-T71.232D,T71.233A-T71.233D,T71.234A-T71.234D,T71.29XA-T71.29XD,T71.9XXA-T71.9XXD, T74.4XXA-T74.4XXD,T75.01XA-T75.01XD,T75.09XA-T75.09XD,T75.1XXA-T75.1XXD,T75.4XXA-T75.4XXD, T78.00XA-T78.00XD,T78.01XA-T78.01XD,T78.02XA-T78.02XD,T78.03XA-T78.03XD,T78.04XA-T78.04XD, T78.05XA-T78.05XD,T78.06XA-T78.06XD,T78.07XA-T78.07XD,T78.08XA-T78.08XD,T78.09XA-T78.09XD, T78.3XXA-T78.3XXD,T78.8XXA-T78.8XXD,T79.0XXA-T79.0XXD,T79.4XXA-T79.4XXD,T79.6XXA-T79.6XXD, T88.2XXA-T88.2XXD,T88.51XA-T88.51XD,T88.6XXA-T88.6XXD,Z45.49,Z46.2,Z46.89,Z47.1

CPT: 20550,20664,21610,23020,23800,23802,24149,24301-24331,24800,24802,25280,25290,25310-25332,25337, 25800,25805,25830,26123,26125,26442,26460,26474,26490,27000-27006,27036,27097-27122,27140,27306, 27307,27325,27326,27390-27400,27430,27435,27605,27606,27612,27676-27692,27705,27870,27871,28005, 28010,28011,28130,28220-28234,28240,28300-28305,28307-28312,28705-28725,28737-28760,29405,29425, 29895,29904-29907,32501,61215,61343,62161,62162,62320-62323,62350,62351,62360-62362,62367-62370, 63600,63610,63650,63655,63685,64642-64647,64763,92531-92548,93792,93793,95873,95874,95990,97012, 97018,97110-97124,97140-97168,97530,97535,97542,97760-97763,98925-98942,98966-98969,99051,99060, 99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513,G0514,G9156

Spinal cord stimulation (63655-63688) is not included on this line when paired with ICD-10-CM category G90.5 Complex regional pain syndrome/reflex sympathetic dystrophy. Chemodenervation with botulinum toxin injection

(CPT 64642-64647) is included on this line for treatment of upper and lower limb spasticity (ICD-10-CM codes G24.02, G24.1, G35, G36.0, I69.03- I69.06 and categories G71, and G80-G83.) CPT codes 62320-3 are only included on Lines 71 and 292 for trials of antispasmodics in preparation for placement of a baclofen pump.

Line: **293**
Condition: ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER (See Guideline Notes 64,65,149)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: D18.09,K76.89,K83.4,Q44.0-Q44.7
CPT: 43260-43265,43273-43278,47010,47400-47490,47533-47540,47542,47544,47554-47556,47564,47570,47600-47620,47701-47900,48548,49185,49324,49325,49405,49421,49422,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **294**
Condition: CANCER OF BRAIN AND NERVOUS SYSTEM (See Guideline Notes 7,11,12,16,64,65,155)
Treatment: LINEAR ACCELERATOR, MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C70.0-C70.9,C71.0-C71.9,C72.0-C72.1,C72.20-C72.9,C79.31-C79.32,C79.49,D42.0-D42.9,D43.0-D43.8,D61.810,G89.3,Z45.49,Z51.0,Z51.11-Z51.12,Z85.841-Z85.848
CPT: 32553,49411,61107,61140,61210,61215,61312-61321,61500-61512,61516-61521,61530,61582,61583,61586,61592,61600-61608,61615,61616,61750,61751,61770-61783,61796-61800,62140-62148,62164,62165,62223,62272,63265,63275-63308,63615-63621,64784-64792,64802-64818,77014,77261-77295,77300-77372,77385-77387,77401-77432,77469,77470,77520-77763,77770-77790,79005-79445,92002-92014,93792,93793,95990,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: A4555,E0766,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

Line: **295**
Condition: APLASTIC ANEMIAS (See Guideline Note 7)
Treatment: MEDICAL THERAPY
ICD-10: D60.0-D60.9,D61.01-D61.3,D61.82-D61.9
CPT: 38242,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9355

Line: **296**
Condition: CATARACT (See Guideline Notes 32,64,65)
Treatment: EXTRACTION OF CATARACT
ICD-10: E08.36,E09.36,E10.36,E11.36,E13.36,H25.011-H25.9,H26.001-H26.33,H26.8,H28,Q12.0-Q12.8,Z96.1
CPT: 65770,66250,66682,66825-66984,66986,66990,67010,92002-92014,92018-92060,92081-92136,92225,92226,92230-92310,92314,92325-92342,92370,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **297**
Condition: AFTER CATARACT
Treatment: DISCISSION, LENS CAPSULE
ICD-10: H26.40,H26.411-H26.499
CPT: 66820-66830,66985-66990,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **298**
Condition: FISTULA INVOLVING FEMALE GENITAL TRACT (See Guideline Notes 64,65)
Treatment: CLOSURE OF FISTULA
ICD-10: N82.0-N82.9
CPT: 44625,44626,44660,46715,50650,50660,50930,51900,51920,57300-57330,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **299**
Condition: VITREOUS DISORDERS (See Guideline Notes 64,65)
Treatment: VITRECTOMY
ICD-10: H43.10-H43.23,H43.811-H43.829,Q14.0
CPT: 67036-67043,67210,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **300**
Condition: CLEFT PALATE AND/OR CLEFT LIP (See Guideline Notes 6,64,65,80)
Treatment: EXCISION AND REPAIR VESTIBULE OF MOUTH, ORTHODONTICS
ICD-10: Q30.2,Q35.1-Q35.9,Q36.0-Q36.9,Q37.0-Q37.9,Q38.0
CPT: 00102,21076,21079,21080,21082,21083,30460,30462,30600,40500-40520,40650-40761,40810-40845,42145,42200-42281,92507,92508,92521-92526,92607-92609,92633,93792,93793,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: D5932,D5933,D5954-D5960,D5987,D5992,D5993,D7111-D7210,D7250,D7260,D7340,D7350,D7912,D8010-D8694,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9152

Line: **301**
Condition: GOUT (See Guideline Notes 6,64,65)
Treatment: MEDICAL THERAPY
ICD-10: M1A.00X0-M1A.9XX1,M10.00,M10.011-M10.9
CPT: 20600-20611,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **302**
Condition: PERTUSSIS AND DIPTHERIA (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A36.0-A36.3,A36.81-A36.9,A37.00-A37.91
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **303**
Condition: THROMBOCYTOPENIA (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: D69.1,D69.3,D69.41-D69.6,D75.82,D82.0
CPT: 38100,38102,38120,90284,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **304**
Condition: VIRAL PNEUMONIA (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: B01.2,B05.2,B06.81,J12.0-J12.3,J12.81-J12.9
CPT: 31600,31601,31820,31825,93792,93793,94640,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **305**
Condition: DISORDERS OF ARTERIES, OTHER THAN CAROTID OR CORONARY (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: I68.2,I75.81-I75.89,I76,I77.0,I77.2-I77.6,I77.89-I77.9,I79.1-I79.8,M31.8-M31.9,N28.0,Q27.1-Q27.2,Q27.31-Q27.39,Q27.8-Q27.9
CPT: 34151,35256,35501-35515,35526,35531,35535-35540,35560,35563,35601-35616,35626-35646,35663,35761,37246,37247,37607,62294,63250-63252,63295,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 306
Condition: PARALYTIC ILEUS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: K56.0,K56.7
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 307
Condition: CIRRHOSIS OF LIVER OR BILIARY TRACT; BUDD-CHIARI SYNDROME; HEPATIC VEIN THROMBOSIS; INTRAHEPATIC VASCULAR MALFORMATIONS; CAROLI'S DISEASE (See Coding Specification Below)
Treatment: LIVER TRANSPLANT, LIVER-KIDNEY TRANSPLANT
ICD-10: I82.0,K65.2,K70.2,K70.30-K70.31,K74.0,K74.3-K74.5,K74.60-K74.69,K76.81,P59.1,P59.20-P59.29,P76.8-P76.9,P78.1,P78.81,P78.84,Q44.6,T86.40-T86.49,Z48.22-Z48.23,Z48.288,Z52.6
CPT: 47133-47147,50300,50323-50365,76776,86825-86835,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Liver-kidney transplant only included on this line for a documented diagnosis of Q44.6 (cystic disease of the liver).

Line: 308
Condition: CHRONIC INFLAMMATORY DISORDER OF ORBIT (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: H05.10,H05.111-H05.129
CPT: 67515,68200,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 309
Condition: CONGENITAL DISLOCATION OF HIP; COXA VARA AND VALGA (See Guideline Notes 6,64,65)
Treatment: SURGICAL TREATMENT
ICD-10: M21.859,Q65.00-Q65.89
CPT: 27001-27006,27036,27140-27165,27179-27185,27256-27259,29305,29325,29861-29863,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 310
Condition: CORNEAL OPACITY AND OTHER DISORDERS OF CORNEA (See Guideline Notes 64,65,168)
Treatment: KERATOPLASTY
ICD-10: E50.4,H17.00-H17.13,H17.811-H17.89,H18.011-H18.13,H18.221-H18.229,H18.40,H18.411-H18.799,Q13.3-Q13.4
CPT: 65286,65400,65436,65450,65710-65757,65772-65785,65920,66250,66825,66985-66990,68371,76514,92002-92014,92018-92060,92072-92136,92225,92226,92230-92310,92313-92342,92370,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 311
Condition: HEARING LOSS - AGE 5 OR UNDER (See Guideline Notes 51,64,65,103,143,154)
Treatment: MEDICAL THERAPY INCLUDING HEARING AIDS, LIMITED SURGICAL THERAPY
ICD-10: H72.00-H72.13,H72.2X1-H72.93,H83.3X1-H83.3X9,H90.0,H90.11-H90.8,H90.A11-H90.A32,H91.01-H91.09,H91.20-H91.3,H91.8X1-H91.93,H93.011-H93.099,H93.211-H93.249,H93.291-H93.8X9,H94.00-H94.83,S09.20XA-S09.20XD,S09.21XA-S09.21XD,S09.22XA-S09.22XD,Z01.12,Z46.1
CPT: 42830,42835,69209,69210,69433,69436,69610-69646,69714-69718,92590-92595,92597,92626,92627,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **312**
Condition: GENDER DYSPHORIA/TRANSEXUALISM (See Guideline Note 127)
Treatment: MEDICAL AND SURGICAL TREATMENT/PSYCHOTHERAPY
ICD-10: F64.0-F64.9,Z87.890
CPT: 17110,17111,17380,19303,19304,19316-19325,19340-19350,53415-53430,54120,54125,54520,54660,54690, 55150-55180,55866,55970,55980,56620,56625,56800-56810,57106,57107,57110,57111,57291-57296,57335, 57426,58150-58180,58260,58262,58275-58291,58353,58356,58541-58544,58550-58554,58563,58570-58573, 58660,58661,58720,58940,90785,90832-90840,90846-90853,90882,90887,93792,93793,97110,97140,97161-97164,97530,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0396,G0397,G0459,G0463-G0467,G0469,G0470,G0490,G0511,G0513,G0514, H0004,H0023,H0032,H0034,H0035,H2010,H2014,H2027,H2032,H2033,S9484

Line: **313**
Condition: DISORDERS INVOLVING THE IMMUNE SYSTEM (See Guideline Notes 64,65,115,156)
Treatment: MEDICAL THERAPY
ICD-10: D69.0,D80.0-D80.9,D81.0-D81.4,D81.6-D81.7,D81.89-D81.9,D82.1-D82.9,D83.0-D83.9,D84.0-D84.9,D89.3, D89.40-D89.49,D89.810-D89.89,M04.1-M04.9,Q89.01-Q89.09,Z51.6
CPT: 36514-36522,86003,86008,86486,90284,93792,93793,95004,95018-95180,96150-96155,98966-98969,99051, 99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490, 99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **314**
Condition: CANCER OF ESOPHAGUS; BARRETT'S ESOPHAGUS WITH DYSPLASIA (See Guideline Notes 7,11,12,19,64,65,144)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C15.3-C15.9,C49.A1,D00.1,D61.810,G89.3,K22.710-K22.719,Z51.0,Z51.11-Z51.12,Z85.01
CPT: 31540,31600,32553,38542,38720,38724,38794,43100-43124,43192,43195,43196,43201,43212-43214,43216-43229,43233,43248,43249,43266,43270,43286-43288,43340,43341,43360,43361,43496,44139-44147,44186, 44204-44208,44213,44300,49411,49442,77014,77261-77295,77300-77307,77321-77370,77385-77387,77402-77427,77469,77470,77761-77763,77770-77790,78811-78816,79005-79445,93792,93793,96150-96155,96377, 96405,96406,96420-96450,96542,96549,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513, G0514,G6001-G6017,S9537

Line: **315**
Condition: CANCER OF LIVER (See Guideline Notes 7,11,12,64,65,78)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C22.0-C22.9,C49.A9,C78.7,D37.6,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.05
CPT: 32553,36260-36262,37243,37617,43260-43265,43274-43277,47120-47130,47370,47371,47380-47382,47533-47540,47542,47562,47600-47620,47711,47712,48150,49411,77014,77261-77295,77300-77370,77385-77387, 77402-77417,77424-77432,77469,77470,79005-79440,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404, 99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G6001-G6017,S9537

Line: **316**
Condition: CANCER OF PANCREAS (See Guideline Notes 7,11,12,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C25.0-C25.3,C25.7-C25.9,D01.7,D61.810,G89.3,Z51.0,Z51.11-Z51.12
CPT: 32553,35251,35281,38747,43260-43265,43273-43278,44130,47542,47721,47741,47760,47785,48140-48155, 49324,49325,49327,49411,49412,49421,49422,64680,77014,77261-77295,77300-77307,77321-77370,77385-77387,77402-77417,77424-77432,77469,77470,79005-79445,93792,93793,96150-96155,96377,96405,96406, 96420-96450,96542,96549,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G6001-G6017,S9537

Line: **317**
Condition: STROKE (See Guideline Notes 6,64,65,90,125)
Treatment: MEDICAL THERAPY
ICD-10: G89.0,I63.00,I63.011-I63.9,I67.0,I67.2,I67.6,I67.81-I67.83,I67.841-I67.89,Z79.01
CPT: 34001,35301,35390,37195,37211,37213-37218,61322,61323,61343,61781,61782,61796-61800,77014,77261-77295,77300,77301,77336,77370-77372,77417,77423,77427-77432,92507,92508,92521-92526,92607-92609,92633,93792,93793,96150-96155,97012,97110-97127,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513-G0515,S9152

Line: **318**
Condition: PURULENT ENDOPHTHALMITIS (See Guideline Notes 64,65)
Treatment: VITRECTOMY
ICD-10: H21.331-H21.339,H33.121-H33.129,H44.001-H44.029,H44.121-H44.129,H44.19
CPT: 65101,65800,66020,66030,67005-67036,67041-67043,67515,68200,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **319**
Condition: FOREIGN BODY IN CORNEA AND CONJUNCTIVAL SAC (See Guideline Notes 64,65)
Treatment: REMOVAL CONJUNCTIVAL FOREIGN BODY
ICD-10: T15.00XA-T15.00XD,T15.01XA-T15.01XD,T15.02XA-T15.02XD,T15.10XA-T15.10XD,T15.11XA-T15.11XD,T15.12XA-T15.12XD,T15.80XA-T15.80XD,T15.81XA-T15.81XD,T15.82XA-T15.82XD,T15.90XA-T15.90XD,T15.91XA-T15.91XD,T15.92XA-T15.92XD
CPT: 65205-65222,67938,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **320**
Condition: OBESITY IN ADULTS AND CHILDREN; OVERWEIGHT STATUS IN ADULTS WITH CARDIOVASCULAR RISK FACTORS (See Guideline Notes 5,8,64,65)
Treatment: BEHAVIORAL INTERVENTIONS INCLUDING INTENSIVE NUTRITIONAL AND PHYSICAL ACTIVITY COUNSELING; BARIATRIC SURGERY
ICD-10: E66.01-E66.9,Z46.51,Z68.30-Z68.45,Z68.54,Z71.3,Z71.82
CPT: 43644,43645,43771-43775,43846-43848,93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498
HCPCS: G0248-G0250,G0396,G0397,G0447,G0463-G0467,G0473,G0490,G0511,G0513,G0514,S2083

Line: **321**
Condition: DERMATOLOGIC HEMANGIOMAS, COMPLICATED (See Guideline Note 13)
Treatment: MEDICAL THERAPY
ICD-10: D18.01
CPT: 11400-11446,12031,12032,13100-13151,17106-17108,21011-21014,21552,21554,21931-21933,22901-22903,23071,23073,24071,24073,25071,25073,26111,26113,27043,27045,27337,27339,27632,27634,28039,28041,40500-40530,40810-40816,40820,41116,41826,42104-42107,42160,42808,69145,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **322**
Condition: OTHER ANEURYSM OF PERIPHERAL ARTERY
Treatment: SURGICAL TREATMENT
ICD-10: I72.1,I72.4,I72.9
CPT: 24900-24931,25900-25931,26910-26952,27590-27598,27880-27889,28800-28825,35001,35002,35011-35021,35141-35152,35572,35682,35683,35875,35876,35903,36002,37609,64802-64818,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **323**
Condition: SIALOADENITIS, ABSCESS, FISTULA OF SALIVARY GLANDS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: K11.20-K11.4
CPT: 40810-40816,42300-42340,42408,42410-42420,42440-42509,42600-42665,93792,93793,98966-98969,99051, 99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490, 99495-99498,99605-99607
HCPCS: D7981-D7983,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513,G0514

Line: **324**
Condition: CYSTICERCOSIS, OTHER CESTODE INFECTION, TRICHINOSIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: B48.8,B68.1-B68.9,B69.0-B69.1,B69.81-B69.9,B70.0-B70.1,B71.0-B71.9,B75
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **325**
Condition: NON-DISSECTING ANEURYSM WITHOUT RUPTURE (See Guideline Notes 64,65)
Treatment: SURGICAL TREATMENT
ICD-10: I71.2,I71.4,I71.6,I71.9,I72.0-I72.9,I77.810-I77.819,I79.0,Q25.43-Q25.44
CPT: 33320-33335,33530,33860-33891,33916,34701-34711,34713,34715,34808-35081,35091,35102,35111-35152, 35188,35301-35372,35500-35518,35526,35531,35535-35540,35560,35563,35572,35601-35671,35682,35683, 35691-35697,35800-35840,35875,35876,35901,35905,35907,36002,36825,36830,37236,37237,37600-37606, 37618,38100,75561-75565,75956-75959,92960-92971,92978-92998,93792-93798,98966-98969,99051,99060, 99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490, G0508-G0511,G0513,G0514

Line: **326**
Condition: SENSORINEURAL HEARING LOSS (See Guideline Note 31)
Treatment: COCHLEAR IMPLANT
ICD-10: H90.3,H90.41-H90.5,H90.A21-H90.A32,Z01.12,Z45.320-Z45.328
CPT: 69930,92562-92565,92571-92577,92590,92591,92601-92604,92626-92633,93792,93793,98966-98969,99051, 99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **327**
Condition: FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION (See Coding Specification Below) (See Guideline Notes 45,57,64,65,145)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: N30.10-N30.11,N30.40-N30.41,N31.0-N31.2,N32.0,N32.3,N32.81,N35.010-N35.9,N36.44-N36.8,N39.490,N40.1, N43.40-N43.42,N48.30-N48.39,N50.1-N50.3,N53.11,N53.13-N53.19,N99.110-N99.114,N99.12,T19.0XXA-T19.0XXD,T19.1XXA-T19.1XXD,T19.4XXA-T19.4XXD,T19.8XXA-T19.8XXD,T19.9XXA-T19.9XXD,Z43.5-Z43.6, Z46.6
CPT: 50706,50845,51040,51100-51102,51525,51700,51705-51715,51800-51845,51880-51980,52001,52214-52240, 52260-52287,52305-52315,52355,52400,52450-52640,52648,52649,53020,53040,53400-53500,53600-53852, 54115,54161,54220-54231,54240,54250,54420-54438,54520,54640,54660-54680,54700,54830-54861,54900, 54901,55400,55520,55600-55680,55801,55821,55831,55862,55865,57220,57287,74445,93792,93793,97140, 97161-97164,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

ICD-10-CM codes N40.1 and N40.3 are only included on this line when post-void residuals are at least 150 cc's.

Line: **328**
Condition: DISSEMINATED INTRAVASCULAR COAGULATION (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: D65
CPT: 25900,25905,25915,25920,25927,26910-26952,27598,27880-27882,27888,27889,28800-28825,30150,54130, 54135,69110,69120,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285, 99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 329
Condition: CANCER OF PROSTATE GLAND (See Guideline Notes 7,11,12,64,65,148)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C61,D07.5,D40.0,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.46
CPT: 32553,38562,38564,38571-38573,38780,49327,49411,49412,51700,52234,52240,52281,52400,52450,52601-52640,52649,53600,53601,54520,54530,54660,55810-55866,58960,77014,77261-77295,77300-77370,77385-77387,77402-77417,77424-77427,77469,77470,77770-77790,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0458,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537,S9560

Line: 330
Condition: SYSTEMIC SCLEROSIS; SJOGREN'S SYNDROME (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: M34.0-M34.2,M34.81-M34.9,M35.01-M35.09
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 331
Condition: ACUTE PROMYELOCYTIC LEUKEMIA
Treatment: BONE MARROW TRANSPLANT
ICD-10: C92.40-C92.42,D61.810,Z48.290,Z52.000-Z52.098,Z52.3
CPT: 36680,38204-38215,38230-38243,86828-86835,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2142,S2150,S9537

Line: 332
Condition: CONDITIONS REQUIRING HYPERBARIC OXYGEN THERAPY (See Guideline Note 107)
Treatment: HYPERBARIC OXYGEN
ICD-10: E08.52,E08.621-E08.622,E09.52,E09.621-E09.622,E10.52,E10.621-E10.622,E11.52,E11.621-E11.622,E13.52,E13.621-E13.622,I70.361-I70.369,I70.461-I70.469,I70.561-I70.569,I70.661-I70.669,I70.761-I70.769,I96,K62.7,L59.8,L88,M27.2,M60.000-M60.005,M60.011-M60.09,M72.6,N30.40-N30.41,O08.0,O88.011-O88.03,Q52.9,S07.0XXA-S07.0XXD,S07.1XXA-S07.1XXD,S07.8XXA-S07.8XXD,S07.9XXA-S07.9XXD,S17.0XXA-S17.0XXD,S17.8XXA-S17.8XXD,S17.9XXA-S17.9XXD,S38.001A-S38.001D,S38.002A-S38.002D,S38.01XA-S38.01XD,S38.02XA-S38.02XD,S38.03XA-S38.03XD,S38.1XXA-S38.1XXD,S38.211A-S38.211D,S38.212A-S38.212D,S38.221A-S38.221D,S38.222A-S38.222D,S38.231A-S38.231D,S38.232A-S38.232D,S38.3XXA-S38.3XXD,S47.1XXA-S47.1XXD,S47.2XXA-S47.2XXD,S47.9XXA-S47.9XXD,S57.00XA-S57.00XD,S57.01XA-S57.01XD,S57.02XA-S57.02XD,S57.80XA-S57.80XD,S57.81XA-S57.81XD,S57.82XA-S57.82XD,S67.00XA-S67.00XD,S67.01XA-S67.01XD,S67.02XA-S67.02XD,S67.10XA-S67.10XD,S67.190A-S67.190D,S67.191A-S67.191D,S67.192A-S67.192D,S67.193A-S67.193D,S67.194A-S67.194D,S67.195A-S67.195D,S67.196A-S67.196D,S67.197A-S67.197D,S67.198A-S67.198D,S67.20XA-S67.20XD,S67.21XA-S67.21XD,S67.22XA-S67.22XD,S67.30XA-S67.30XD,S67.31XA-S67.31XD,S67.32XA-S67.32XD,S67.40XA-S67.40XD,S67.41XA-S67.41XD,S67.42XA-S67.42XD,S67.90XA-S67.90XD,S67.91XA-S67.91XD,S67.92XA-S67.92XD,S77.00XA-S77.00XD,S77.01XA-S77.01XD,S77.02XA-S77.02XD,S77.10XA-S77.10XD,S77.11XA-S77.11XD,S77.12XA-S77.12XD,S77.20XA-S77.20XD,S77.21XA-S77.21XD,S77.22XA-S77.22XD,S87.00XA-S87.00XD,S87.01XA-S87.01XD,S87.02XA-S87.02XD,S87.80XA-S87.80XD,S87.81XA-S87.81XD,S87.82XA-S87.82XD,S97.00XA-S97.00XD,S97.01XA-S97.01XD,S97.02XA-S97.02XD,S97.101A-S97.101D,S97.102A-S97.102D,S97.109A-S97.109D,S97.111A-S97.111D,S97.112A-S97.112D,S97.119A-S97.119D,S97.121A-S97.121D,S97.122A-S97.122D,S97.129A-S97.129D,S97.80XA-S97.80XD,S97.81XA-S97.81XD,S97.82XA-S97.82XD,T57.1X1A-T57.1X1D,T57.1X2A-T57.1X2D,T57.1X3A-T57.1X3D,T57.1X4A-T57.1X4D,T57.3X1A-T57.3X1D,T57.3X2A-T57.3X2D,T57.3X3A-T57.3X3D,T57.3X4A-T57.3X4D,T58.01XA-T58.01XD,T58.02XA-T58.02XD,T58.03XA-T58.03XD,T58.04XA-T58.04XD,T58.11XA-T58.11XD,T58.12XA-T58.12XD,T58.13XA-T58.13XD,T58.14XA-T58.14XD,T58.2X1A-T58.2X1D,T58.2X2A-T58.2X2D,T58.2X3A-T58.2X3D,T58.2X4A-T58.2X4D,T58.8X1A-T58.8X1D,T58.8X2A-T58.8X2D,T58.8X3A-T58.8X3D,T58.8X4A-T58.8X4D,T58.91XA-T58.91XD,T58.92XA-T58.92XD,T58.93XA-T58.93XD,T58.94XA-T58.94XD,T59.0X1A-T59.0X1D,T59.0X2A-T59.0X2D,T59.0X3A-T59.0X3D,T59.0X4A-T59.0X4D,T59.1X1A-T59.1X1D,T59.1X2A-T59.1X2D,T59.1X3A-T59.1X3D,T59.1X4A-T59.1X4D,T59.2X1A-T59.2X1D,T59.2X2A-T59.2X2D,T59.2X3A-T59.2X3D,T59.2X4A-T59.2X4D,T59.3X1A-T59.3X1D,T59.3X2A-T59.3X2D,T59.3X3A-T59.3X3D,T59.3X4A-T59.3X4D,T59.4X1A-T59.4X1D,T59.4X2A-T59.4X2D,T59.4X3A-T59.4X3D,T59.4X4A-T59.4X4D,T59.5X1A-T59.5X1D,T59.5X2A-T59.5X2D,T59.5X3A-T59.5X3D,T59.5X4A-T59.5X4D,T59.6X1A-T59.6X1D,T59.6X2A-T59.6X2D,T59.6X3A-T59.6X3D,T59.6X4A-T59.6X4D,T59.7X1A-T59.7X1D,T59.7X2A-T59.7X2D,T59.7X3A-T59.7X3D,T59.7X4A-T59.7X4D,T59.811A-T59.811D,T59.812A-T59.812D,T59.813A-T59.813D,T59.814A-T59.814D,T59.891A-T59.891D,T59.892A-T59.892D,T59.893A-T59.893D,T59.894A-T59.894D,T59.91XA-T59.91XD,T59.92XA-T59.92XD,T59.93XA-T59.93XD,T59.94XA-T59.94XD,T66.XXXA-T66.XXXD,T70.3XXA-T70.3XXD,T79.0XXA-T79.0XXD,T79.A0XA-T79.A0XD,T79.A11A-T79.A11D,T79.A12A-T79.A12D,T79.A19A-T79.A19D,T79.A21A-T79.A21D,T79.A22A-T79.A22D,T79.A29A-T79.A29D,T79.A3XA-T79.A3XD,T79.A9XA-T79.A9XD,T80.0XXA-T80.0XXD,T82.898A-T82.898D,T82.9XXA-T82.9XXD,T83.89XA-T83.89XD,T83.9XXA-T83.9XXD,T84.89XA-T84.89XD,T84.9XXA-T84.9XXD,

T85.9XXA-T85.9XXD,T86.820-T86.829
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99183,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0277,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **333**
Condition: BENIGN CEREBRAL CYSTS
Treatment: DRAINAGE
ICD-10: B69.0,G93.0,G96.12-G96.19,M25.08
CPT: 61120,61150,61151,61314-61316,61516,61522,61524,61781,61782,62223,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **334**
Condition: ALCOHOLIC FATTY LIVER OR ALCOHOLIC HEPATITIS, CIRRHOSIS OF LIVER (See Guideline Notes 64,65,77)
Treatment: MEDICAL THERAPY
ICD-10: K70.0,K70.10-K70.9,K71.3-K71.4,K71.50-K71.7,K72.10-K72.91,K74.0,K74.3-K74.5,K74.60-K74.69,K76.1,K76.6,K76.89
CPT: 37182,37183,93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **335**
Condition: SCLERITIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A18.51,A50.01,A50.30,A50.39,A51.43,A52.71,B58.00,B58.09,H15.001-H15.099,H15.121-H15.89
CPT: 66130,66220-66250,67250,67255,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **336**
Condition: RUBEOSIS AND OTHER DISORDERS OF THE IRIS (See Guideline Notes 64,65)
Treatment: LASER SURGERY
ICD-10: H21.1X1-H21.1X9,H21.40-H21.43,H21.501-H21.569,Q13.1
CPT: 65870,65875,66170,66680,66682,66720,67228,67500,76514,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **337**
Condition: WOUND OF EYE GLOBE (See Guideline Notes 64,65)
Treatment: SURGICAL REPAIR
ICD-10: S05.20XA-S05.20XD,S05.21XA-S05.21XD,S05.22XA-S05.22XD,S05.30XA-S05.30XD,S05.31XA-S05.31XD,S05.32XA-S05.32XD,S05.50XA-S05.50XD,S05.51XA-S05.51XD,S05.52XA-S05.52XD,S05.60XA-S05.60XD,S05.61XA-S05.61XD,S05.62XA-S05.62XD,S05.70XA-S05.70XD,S05.71XA-S05.71XD,S05.72XA-S05.72XD,S05.8X1A-S05.8X1D,S05.8X2A-S05.8X2D,S05.8X9A-S05.8X9D,S05.90XA-S05.90XD,S05.91XA-S05.91XD,S05.92XA-S05.92XD
CPT: 65105,65235-65273,65280,65285,65290,66680,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **338**
Condition: ACUTE NECROSIS OF LIVER (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: K71.0,K71.10-K71.2,K71.8-K71.9,K72.00-K72.01,K75.2-K75.3,K75.89,K76.2,K76.89
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **339**
Condition: CHRONIC KIDNEY DISEASE (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY INCLUDING DIALYSIS
ICD-10: B52.0,E08.21-E08.29,E09.21-E09.29,E10.21-E10.29,E11.21-E11.29,E13.21-E13.29,E88.3,I12.0-I12.9,N02.0-N02.9,N03.0-N03.9,N04.0-N04.9,N05.2-N05.9,N06.0-N06.9,N07.0-N07.9,N08,N14.0-N14.4,N15.0,N15.8-N15.9,N16,N18.1-N18.5,N18.9,N25.0-N25.1,N25.89,N26.1,N26.9,N27.0-N27.9,N28.9,N29,Z49.01-Z49.32
CPT: 36514,36516,36800-36821,36825-36838,36901-36909,49324-49326,49421,49422,49435,49436,90935-90947,90989-90997,93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9339,S9355,S9537

Line: **340**
Condition: HEREDITARY HEMORRHAGIC TELANGIECTASIA (See Guideline Note 65)
Treatment: EXCISION
ICD-10: I78.0
CPT: 11400-11426,45382,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **341**
Condition: RHEUMATIC FEVER (See Guideline Notes 6,64,65)
Treatment: MEDICAL THERAPY
ICD-10: I00,I02.9
CPT: 93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **342**
Condition: OTHER AND UNSPECIFIED ANTERIOR PITUITARY HYPERFUNCTION, BENIGN NEOPLASM OF THYROID GLAND AND OTHER ENDOCRINE GLANDS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES RADIATION THERAPY
ICD-10: D34,D35.00-D35.02,D35.2-D35.9,E16.3-E16.9,E22.1-E22.9,E23.3,E34.4,G89.3,Z51.0
CPT: 32553,48140,48155,49411,60200-60240,60270,60271,60512,60600-60650,61548,62100,77338,77402,79005-79445,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **343**
Condition: DENTAL CONDITIONS (E.G., CARIES, FRACTURED TOOTH) (See Guideline Notes 91,123)
Treatment: BASIC RESTORATIVE (E.G., COMPOSITE RESTORATIONS FOR ANTERIOR TEETH, AMALGAM RESTORATIONS FOR POSTERIOR TEETH)
ICD-10: K02.3,K02.51-K02.9,K03.2,K03.89,K08.530-K08.539
HCPCS: D1354,D2140-D2394,D2930-D2933,D2941,D2950,D2951,D2954,D2957,D2980,D6980

Line: **344**
Condition: DENTAL CONDITIONS (E.G., SEVERE CARIES, INFECTION) (See Guideline Notes 34,48)
Treatment: ORAL SURGERY (I.E., EXTRACTIONS AND OTHER INTRAORAL SURGICAL PROCEDURES)
ICD-10: E08.630-E08.638,E09.630-E09.638,E10.630-E10.638,E11.630-E11.638,E13.630-E13.638,K02.3,K02.51-K02.9
CPT: 41870,41872
HCPCS: D6096,D6100,D7210-D7251,D7310-D7321,D7450,D7451,D7465,D7471,D7540,D7550,D7960,D7963,D7971,D9930

Line: **345**
Condition: NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS (See Guideline Notes 6,64,65,90)
Treatment: MEDICAL THERAPY
ICD-10: A33,A50.40,A50.43,A50.45,A52.10,A52.12-A52.15,A52.17-A52.19,A52.3,A81.00-A81.83,A87.1-A87.2,A88.8,A89,C32.8-C32.9,C70.0-C70.9,C71.0-C71.9,C72.0-C72.1,C72.20-C72.9,D33.9,D81.3,D81.5,E00.0-E00.9,E45,E70.0-E70.1,E70.20-E70.29,E70.330-E70.331,E70.8-E70.9,E71.0,E71.110-E71.548,E72.00,E72.02-E72.51,E72.59-E72.9,E74.00-E74.09,E74.20-E74.29,E75.00-E75.09,E75.11-E75.23,E75.240-E75.6,E76.01-E76.1,E76.210-E76.9,E77.0-E77.9,E78.70-E78.9,E79.1-E79.9,E80.0-E80.1,E80.20-E80.3,E83.00-E83.09,E88.2,E88.40-E88.49,E88.89,F01.50-F01.51,F03.90-F03.91,F06.1,F06.8,F07.89,F70-F79,F80.0-F80.4,F80.81-F80.89,F84.0-F84.3,F84.8,F98.5,G04.1,G04.81-G04.91,G10,G11.0-G11.4,G11.9,G12.0-G12.1,G12.21-G12.9,G13.1-G13.8,G14-G20,G21.0,G21.11-G21.9,G23.0-G23.9,G24.1-G24.2,G24.8,G25.4-G25.5,G25.82,G25.9,G30.0-G30.8,G31.01-G31.83,G31.85-G31.9,G32.0,G32.81-G32.89,G35,G36.0-G36.9,G37.0-G37.9,G40.011-G40.019,G40.111-G40.119,

G40.211-G40.219,G40.311-G40.319,G40.411-G40.419,G40.811,G40.89,G40.911-G40.919,G60.0-G60.8,G61.0-G61.1,G61.81-G61.89,G62.0-G62.2,G62.81-G62.89,G64,G71.0,G71.11-G71.8,G72.0-G72.3,G72.41-G72.89,G73.7,G80.0-G80.9,G81.00-G81.94,G82.20-G82.54,G83.0,G83.30-G83.9,G90.01-G90.1,G90.3-G90.4,G91.0-G91.9,G92,G93.0-G93.1,G93.40-G93.81,G93.89,G94,G95.0,G95.11-G95.29,G95.89,G97.0,G97.2,G97.31-G97.32,G97.48-G97.49,G97.61-G97.82,G99.0-G99.8,H49.811-H49.819,H93.25,I61.0-I61.9,I62.00-I62.9,I63.30,I63.311-I63.312,I63.319-I63.322,I63.329-I63.332,I63.339-I63.342,I63.349-I63.412,I63.419-I63.422,I63.429-I63.432,I63.439-I63.442,I63.449-I63.512,I63.519-I63.522,I63.529-I63.532,I63.539-I63.542,I63.549-I63.9,I67.3,I67.81-I67.83,I67.841-I67.89,I69.010-I69.018,I69.020-I69.028,I69.051-I69.090,I69.092,I69.110-I69.118,I69.120-I69.128,I69.151-I69.190,I69.192,I69.210-I69.218,I69.220-I69.228,I69.251-I69.290,I69.292,I69.310-I69.318,I69.320-I69.328,I69.351-I69.390,I69.392,I69.810-I69.818,I69.820-I69.828,I69.851-I69.890,I69.892,I69.910-I69.918,I69.920-I69.928,I69.951-I69.990,I69.992,I97.810-I97.821,M62.3,M62.58-M62.59,M62.89,P07.00-P07.39,P10.0-P10.9,P11.0,P11.2,P11.5-P11.9,P19.0-P19.9,P24.00-P24.21,P24.80-P24.9,P35.0-P35.9,P37.0-P37.9,P39.2,P50.0-P50.9,P51.0-P51.9,P52.0-P52.1,P52.21-P52.9,P54.1-P54.9,P55.1-P55.9,P56.0,P56.90-P56.99,P57.0,P91.2,P91.60-P91.63,P96.81,Q00.0-Q00.2,Q01.0-Q01.9,Q02,Q03.0-Q03.9,Q04.0-Q04.9,Q05.0-Q05.9,Q06.0-Q06.9,Q07.00-Q07.9,Q74.3,Q77.3,Q77.6,Q78.0-Q78.3,Q78.5-Q78.6,Q85.1,Q86.0-Q86.8,Q87.1-Q87.3,Q87.40,Q87.410-Q87.89,Q89.4-Q89.8,Q90.0-Q90.9,Q91.0-Q91.7,Q92.0-Q92.5,Q92.62-Q92.9,Q93.0-Q93.7,Q93.81-Q93.9,Q95.2-Q95.8,Q96.0-Q96.9,Q97.0-Q97.8,Q98.0-Q98.3,Q98.5-Q98.8,Q99.0-Q99.8,R13.10-R13.19,R41.4,R41.81,R53.2,R54,S06.370A-S06.370D,S06.810A-S06.810D,S06.811A-S06.811D,S06.812A-S06.812D,S06.813A-S06.813D,S06.814A-S06.814D,S06.815A-S06.815D,S06.816A-S06.816D,S06.817A-S06.819D,S06.820A-S06.820D,S06.821A-S06.821D,S06.822A-S06.822D,S06.823A-S06.823D,S06.824A-S06.824D,S06.825A-S06.825D,S06.826A-S06.826D,S06.827A-S06.829D,S06.890A-S06.890D,S06.891A-S06.891D,S06.892A-S06.892D,S06.893A-S06.893D,S06.894A-S06.894D,S06.895A-S06.895D,S06.896A-S06.896D,S06.897A-S06.899D,S06.9X0A-S06.9X0D,S06.9X1A-S06.9X1D,S06.9X2A-S06.9X2D,S06.9X3A-S06.9X3D,S06.9X4A-S06.9X4D,S06.9X5A-S06.9X5D,S06.9X6A-S06.9X6D,S06.9X7A-S06.9X9D,S14.0XXA-S14.0XXD,S14.101A-S14.101D,S14.102A-S14.102D,S14.103A-S14.103D,S14.104A-S14.104D,S14.105A-S14.105D,S14.106A-S14.106D,S14.107A-S14.107D,S14.108A-S14.108D,S14.109A-S14.109D,S14.111A-S14.111D,S14.112A-S14.112D,S14.113A-S14.113D,S14.114A-S14.114D,S14.115A-S14.115D,S14.116A-S14.116D,S14.117A-S14.117D,S14.118A-S14.118D,S14.119A-S14.119D,S14.121A-S14.121D,S14.122A-S14.122D,S14.123A-S14.123D,S14.124A-S14.124D,S14.125A-S14.125D,S14.126A-S14.126D,S14.127A-S14.127D,S14.128A-S14.128D,S14.129A-S14.129D,S14.131A-S14.131D,S14.132A-S14.132D,S14.133A-S14.133D,S14.134A-S14.134D,S14.135A-S14.135D,S14.136A-S14.136D,S14.137A-S14.137D,S14.138A-S14.138D,S14.139A-S14.139D,S14.141A-S14.141D,S14.142A-S14.142D,S14.143A-S14.143D,S14.144A-S14.144D,S14.145A-S14.145D,S14.146A-S14.146D,S14.147A-S14.147D,S14.148A-S14.148D,S14.149A-S14.149D,S14.151A-S14.151D,S14.152A-S14.152D,S14.153A-S14.153D,S14.154A-S14.154D,S14.155A-S14.155D,S14.156A-S14.156D,S14.157A-S14.157D,S14.158A-S14.158D,S14.159A-S14.159D,S14.2XXA-S14.2XXD,S14.3XXA-S14.3XXD,S24.0XXA-S24.0XXD,S24.101A-S24.101D,S24.102A-S24.102D,S24.103A-S24.103D,S24.104A-S24.104D,S24.109A-S24.109D,S24.111A-S24.111D,S24.112A-S24.112D,S24.113A-S24.113D,S24.114A-S24.114D,S24.119A-S24.119D,S24.131A-S24.131D,S24.132A-S24.132D,S24.133A-S24.133D,S24.134A-S24.134D,S24.139A-S24.139D,S24.141A-S24.141D,S24.142A-S24.142D,S24.143A-S24.143D,S24.144A-S24.144D,S24.149A-S24.149D,S24.151A-S24.151D,S24.152A-S24.152D,S24.153A-S24.153D,S24.154A-S24.154D,S24.159A-S24.159D,S24.2XXA-S24.2XXD,S34.01XA-S34.01XD,S34.02XA-S34.02XD,S34.101A-S34.101D,S34.102A-S34.102D,S34.103A-S34.103D,S34.104A-S34.104D,S34.105A-S34.105D,S34.109A-S34.109D,S34.111A-S34.111D,S34.112A-S34.112D,S34.113A-S34.113D,S34.114A-S34.114D,S34.115A-S34.115D,S34.119A-S34.119D,S34.121A-S34.121D,S34.122A-S34.122D,S34.123A-S34.123D,S34.124A-S34.124D,S34.125A-S34.125D,S34.129A-S34.129D,S34.131A-S34.131D,S34.132A-S34.132D,S34.139A-S34.139D,S34.21XA-S34.21XD,S34.22XA-S34.22XD,S34.3XXA-S34.3XXD,S34.4XXA-S34.4XXD,T40.0X1A-T40.0X1D,T40.0X2A-T40.0X2D,T40.0X3A-T40.0X3D,T40.0X4A-T40.0X4D,T40.1X1A-T40.1X1D,T40.1X2A-T40.1X2D,T40.1X3A-T40.1X3D,T40.1X4A-T40.1X4D,T40.2X1A-T40.2X1D,T40.2X2A-T40.2X2D,T40.2X3A-T40.2X3D,T40.2X4A-T40.2X4D,T40.3X1A-T40.3X1D,T40.3X2A-T40.3X2D,T40.3X3A-T40.3X3D,T40.3X4A-T40.3X4D,T40.4X1A-T40.4X1D,T40.4X2A-T40.4X2D,T40.4X3A-T40.4X3D,T40.4X4A-T40.4X4D,T40.5X1A-T40.5X1D,T40.5X2A-T40.5X2D,T40.5X3A-T40.5X3D,T40.5X4A-T40.5X4D,T40.601A-T40.601D,T40.602A-T40.602D,T40.603A-T40.603D,T40.604A-T40.604D,T40.691A-T40.691D,T40.692A-T40.692D,T40.693A-T40.693D,T40.694A-T40.694D,T40.7X1A-T40.7X1D,T40.7X2A-T40.7X2D,T40.7X3A-T40.7X3D,T40.7X4A-T40.7X4D,T40.8X1A-T40.8X1D,T40.8X2A-T40.8X2D,T40.8X3A-T40.8X3D,T40.8X4A-T40.8X4D,T40.901A-T40.901D,T40.902A-T40.902D,T40.903A-T40.903D,T40.904A-T40.904D,T40.991A-T40.991D,T71.111A-T71.111D,T71.112A-T71.112D,T71.113A-T71.113D,T71.114A-T71.114D,T71.121A-T71.121D,T71.122A-T71.122D,T71.123A-T71.123D,T71.124A-T71.124D,T71.131A-T71.131D,T71.132A-T71.132D,T71.133A-T71.133D,T71.134A-T71.134D,T71.141A-T71.141D,T71.143A-T71.143D,T71.144A-T71.144D,T71.151A-T71.151D,T71.152A-T71.152D,T71.153A-T71.153D,T71.154A-T71.154D,T71.161A-T71.161D,T71.162A-T71.162D,T71.163A-T71.163D,T71.164A-T71.164D,T71.191A-T71.191D,T71.192A-T71.192D,T71.193A-T71.193D,T71.194A-T71.194D,T71.20XA-T71.20XD,T71.21XA-T71.21XD,T71.221A-T71.221D,T71.222A-T71.222D,T71.223A-T71.223D,T71.224A-T71.224D,T71.231A-T71.231D,T71.232A-T71.232D,T71.233A-T71.233D,T71.234A-T71.234D,T71.29XA-T71.29XD,T71.9XXA-T71.9XXD,T74.4XXA-T74.4XXD,T75.01XA-T75.01XD,T75.09XA-T75.09XD,T75.1XXA-T75.1XXD,T75.4XXA-T75.4XXD,T78.00XA-T78.00XD,T78.01XA-T78.01XD,T78.02XA-T78.02XD,T78.03XA-T78.03XD,T78.04XA-T78.04XD,T78.05XA-T78.05XD,T78.06XA-T78.06XD,T78.07XA-T78.07XD,T78.08XA-T78.08XD,T78.09XA-T78.09XD,T78.3XXA-T78.3XXD,T78.8XXA-T78.8XXD,T79.0XXA-T79.0XXD,T79.4XXA-T79.4XXD,T79.6XXA-T79.6XXD,T88.2XXA-T88.2XXD,T88.51XA-T88.51XD,T88.6XXA-T88.6XXD,Z90.02

CPT: 21084,31611,61215,92507,92508,92521-92524,92607-92609,92633,93792,93793,97012,97110-97127,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513-G0515,S9152

Line: 346
Condition: CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS (See Guideline Notes 37,60,64,65,100,101)
Treatment: SURGICAL THERAPY
ICD-10: G83.4,M43.10-M43.19,M47.011-M47.27,M48.00-M48.05,M48.061-M48.08,M50.00-M50.01,M50.020-M50.11,M51.04-M51.17,M53.2X1-M53.2X9,M54.10-M54.18,Q06.8,Q76.2
CPT: 20660-20665,20930-20938,21720,21725,22206-22226,22532-22865,29000-29046,29710,29720,62287,63001-63091,63170,63180-63200,63270-63273,63295-63610,63650,63655,63685,93792,93793,96150-96155,97110-97124,97140-97168,97530,97535,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487,99489,99495,99496,99605-99607
HCPCS: G0157-G0160,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0508-G0511,G0513,G0514,S2350,S2351

Line: 347
Condition: CARDIAC ARRHYTHMIAS (See Guideline Notes 49,64,65,146)
Treatment: MEDICAL THERAPY, PACEMAKER
ICD-10: I44.0-I44.2,I44.30-I44.7,I45.0,I45.10-I45.9,I47.1,I47.9,I48.0-I48.4,I48.91-I48.92,I49.1-I49.2,I49.40-I49.9,I97.120-I97.121,R00.1,Z45.010-Z45.09,Z79.01
CPT: 33202-33229,33233-33238,33250-33261,33265,33266,92960-92971,92978-92998,93279-93284,93286-93289,93292-93296,93600-93642,93650-93657,93724,93745,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,K0606-K0609

Line: 348
Condition: MILD/MODERATE BIRTH TRAUMA FOR BABY (See Guideline Notes 6,64,65)
Treatment: MEDICAL THERAPY
ICD-10: P11.1,P11.3-P11.4,P12.0-P12.1,P12.3-P12.4,P12.81-P12.9,P13.0-P13.9,P14.0-P14.9,P15.0-P15.9
CPT: 22830,67036-67043,67208,67210,67220,67227-67229,67515,92002-92014,92018-92060,92081-92136,92225-92287,93792,93793,96154,96155,97012,97110-97124,97140-97168,97530,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 349
Condition: NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE (See Guideline Notes 64,65)
Treatment: SURGICAL TREATMENT
ICD-10: E08.51,E09.51,E10.51,E11.51,E13.51,I70.201-I70.209,I70.231-I70.25,I70.291-I70.309,I70.331-I70.35,I70.391-I70.409,I70.431-I70.45,I70.491-I70.509,I70.531-I70.55,I70.591-I70.609,I70.631-I70.65,I70.691-I70.709,I70.731-I70.75,I70.791-I70.92,I74.2-I74.4,I74.9,I75.011-I75.029,I77.1
CPT: 13160,34101,34111,34201,34203,35081,35256,35286,35302-35321,35351-35372,35500,35510,35512,35516-35525,35533,35539-35558,35565-35587,35606,35621,35623,35646-35661,35665-35671,35682-35686,35700-35761,35860,35875-35881,35903,36002,37184-37186,37211,37213,37214,37220-37235,37246-37249,37609,64802-64818,64821-64823,93668,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 350
Condition: SARCOIDOSIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: D86.0-D86.3,D86.81-D86.82,D86.84-D86.9
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 351
Condition: STRABISMUS DUE TO NEUROLOGIC DISORDER (See Coding Specification Below) (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: H49.00-H49.43,H49.881-H49.9,H51.20-H51.23
CPT: 15822,15823,65778-65782,66820-66830,66985,66986,67311-67345,67710,67875,67880,67900-67912,67961,67971,68135,68320-68328,68335,68340,68371,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Chemodenervation with botulinum toxin injection (CPT 67345) is included on this line for the treatment of strabismus due to other neurological disorders (ICD-10 H50.89).

Line: 352
Condition: URINARY SYSTEM CALCULUS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: N20.0-N20.9,N21.0-N21.9,N22
CPT: 50060-50081,50130,50382-50389,50395,50432-50435,50553,50557,50561,50572,50580,50590,50600,50605,50610-50630,50693-50700,50715,50900,50945,50947,50961-50972,50976,50980,51050-51065,51102,51700,52310-52325,52330-52334,52352,52353,52356,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 353
Condition: STRUCTURAL CAUSES OF AMENORRHEA (See Guideline Note 65)
Treatment: SURGICAL TREATMENT
ICD-10: N85.7,N89.5-N89.7,N92.5,N93.8,N99.2,Q51.0,Q51.5,Q51.7,Q51.820-Q51.9,Q52.0,Q52.10-Q52.11,Q52.121-Q52.8,Z43.7
CPT: 56441,56442,56700,56800,57130,57291-57295,57400,57426,57800,58120,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 354
Condition: PENETRATING WOUND OF ORBIT (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: H05.50-H05.53,S01.101A-S01.101D,S01.102A-S01.102D,S01.109A-S01.109D,S05.40XA-S05.40XD,S05.41XA-S05.41XD,S05.42XA-S05.42XD
CPT: 12011,12013,12051,12052,13132,13151,13152,67405-67414,67420-67445,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 355
Condition: CLOSED FRACTURE OF EXTREMITIES (EXCEPT MINOR TOES) (See Guideline Notes 6,64,65)
Treatment: OPEN OR CLOSED REDUCTION
ICD-10: M24.029,M80.00XA,M80.011A-M80.011G,M80.012A-M80.012G,M80.019A-M80.019G,M80.021A-M80.021G,M80.022A-M80.022G,M80.029A-M80.029G,M80.031A-M80.031G,M80.032A-M80.032G,M80.039A-M80.039G,M80.041A-M80.041G,M80.042A-M80.042G,M80.049A-M80.049G,M80.051A-M80.051G,M80.052A-M80.052G,M80.059A-M80.059G,M80.061A-M80.061G,M80.062A-M80.062G,M80.069A-M80.069G,M80.071A-M80.071G,M80.072A-M80.072G,M80.079A-M80.079G,M80.80XA,M80.811A-M80.811G,M80.812A-M80.812G,M80.819A-M80.819G,M80.821A-M80.821G,M80.822A-M80.822G,M80.829A-M80.829G,M80.831A-M80.831G,M80.832A-M80.832G,M80.839A-M80.839G,M80.841A-M80.841G,M80.842A-M80.842G,M80.849A-M80.849G,M80.851A-M80.851G,M80.852A-M80.852G,M80.859A-M80.859G,M80.861A-M80.861G,M80.862A-M80.862G,M80.869A-M80.869G,M80.871A-M80.871G,M80.872A-M80.872G,M80.879A-M80.879G,M84.30XA,M84.311A-M84.311G,M84.312A-M84.312G,M84.319A-M84.319G,M84.321A-M84.321G,M84.322A-M84.322G,M84.329A-M84.329G,M84.331A-M84.331G,M84.332A-M84.332G,M84.333A-M84.333G,M84.334A-M84.334G,M84.339A-M84.339G,M84.341A-M84.341G,M84.342A-M84.342G,M84.343A-M84.343G,M84.344A-M84.344G,M84.345A-M84.345G,M84.346A-M84.346G,M84.351A-M84.351G,M84.352A-M84.352G,M84.353A-M84.353G,M84.361A-M84.361G,M84.362A-M84.362G,M84.363A-M84.363G,M84.364A-M84.364G,M84.369A-M84.369G,M84.371A-M84.371G,M84.372A-M84.372G,M84.373A-M84.373G,M84.374A-M84.374G,M84.375A-M84.375G,M84.376A-M84.376G,M84.38XA,M84.40XA,M84.411A-M84.411G,M84.412A-M84.412G,M84.419A-M84.419G,M84.421A-M84.421G,M84.422A-M84.422G,M84.429A-M84.429G,M84.431A-M84.431G,M84.432A-M84.432G,M84.433A-M84.433G,M84.434A-M84.434G,M84.439A-M84.439G,M84.441A-M84.441G,M84.442A-M84.442G,M84.443A-M84.443G,M84.444A-M84.444G,M84.445A-M84.445G,M84.446A-M84.446G,M84.451A-M84.451G,M84.452A-M84.452G,M84.453A-M84.453G,M84.461A-M84.461G,M84.462A-M84.462G,M84.463A-M84.463G,M84.464A-M84.464G,M84.469A-M84.469G,M84.471A-M84.471G,M84.472A-M84.472G,M84.473A-M84.473G,M84.474A-M84.474G,M84.475A-M84.475G,M84.476A-M84.476G,M84.48XA,M84.50XA,M84.511A-M84.511G,M84.512A-M84.512G,

M84.519A-M84.519G,M84.521A-M84.521G,M84.522A-M84.522G,M84.529A-M84.529G,M84.531A-M84.531G,
M84.532A-M84.532G,M84.533A-M84.533G,M84.534A-M84.534G,M84.539A-M84.539G,M84.541A-M84.541G,
M84.542A-M84.542G,M84.549A-M84.549G,M84.551A-M84.551G,M84.552A-M84.552G,M84.553A-M84.553G,
M84.561A-M84.561G,M84.562A-M84.562G,M84.563A-M84.563G,M84.564A-M84.564G,M84.569A-M84.569G,
M84.571A-M84.571G,M84.572A-M84.572G,M84.573A-M84.573G,M84.574A-M84.574G,M84.575A-M84.575G,
M84.576A-M84.576G,M84.58XD-M84.58XG,M84.60XA,M84.611A-M84.611G,M84.612A-M84.612G,M84.619A-
M84.619G,M84.621A-M84.621G,M84.622A-M84.622G,M84.629A-M84.629G,M84.631A-M84.631G,M84.632A-
M84.632G,M84.633A-M84.633G,M84.634A-M84.634G,M84.639A-M84.639G,M84.641A-M84.641G,M84.642A-
M84.642G,M84.649A-M84.649G,M84.651A-M84.651G,M84.652A-M84.652G,M84.653A-M84.653G,M84.661A-
M84.661G,M84.662A-M84.662G,M84.663A-M84.663G,M84.664A-M84.664G,M84.669A-M84.669G,M84.671A-
M84.671G,M84.672A-M84.672G,M84.673A-M84.673G,M84.674A-M84.674G,M84.675A-M84.675G,M84.676A-
M84.676G,M84.750A-M84.750G,M84.751A-M84.751G,M84.752A-M84.752G,M84.753A-M84.753G,M84.754A-
M84.754G,M84.755A-M84.755G,M84.756A-M84.756G,M84.757A-M84.757G,M84.758A-M84.758G,M84.759A-
M84.759G,M93.001-M93.033,S32.446D,S42.001A,S42.001D-S42.001G,S42.002A,S42.002D-S42.002G,
S42.009A,S42.009D-S42.009G,S42.011A,S42.011D-S42.011G,S42.012A,S42.012D-S42.012G,S42.013A,
S42.013D-S42.013G,S42.014A,S42.014D-S42.014G,S42.015A,S42.015D-S42.015G,S42.016A,S42.016D-
S42.016G,S42.017A,S42.017D-S42.017G,S42.018A,S42.018D-S42.018G,S42.019A,S42.019D-S42.019G,
S42.021A,S42.021D-S42.021G,S42.022A,S42.022D-S42.022G,S42.023A,S42.023D-S42.023G,S42.024A,
S42.024D-S42.024G,S42.025A,S42.025D-S42.025G,S42.026A,S42.026D-S42.026G,S42.031A,S42.031D-
S42.031G,S42.032A,S42.032D-S42.032G,S42.033A,S42.033D-S42.033G,S42.034A,S42.034D-S42.034G,
S42.035A,S42.035D-S42.035G,S42.036A,S42.036D-S42.036G,S42.101A,S42.101D-S42.101G,S42.102A,
S42.102D-S42.102G,S42.109A,S42.109D-S42.109G,S42.111A,S42.111D-S42.111G,S42.112A,S42.112D-
S42.112G,S42.113A,S42.113D-S42.113G,S42.114A,S42.114D-S42.114G,S42.115A,S42.115D-S42.115G,
S42.116A,S42.116D-S42.116G,S42.121A,S42.121D-S42.121G,S42.122A,S42.122D-S42.122G,S42.123A,
S42.123D-S42.123G,S42.124A,S42.124D-S42.124G,S42.125A,S42.125D-S42.125G,S42.126A,S42.126D-
S42.126G,S42.131A,S42.131D-S42.131G,S42.132A,S42.132D-S42.132G,S42.133A,S42.133D-S42.133G,
S42.134A,S42.134D-S42.134G,S42.135A,S42.135D-S42.135G,S42.136A,S42.136D-S42.136G,S42.141A,
S42.141D-S42.141G,S42.142A,S42.142D-S42.142G,S42.143A,S42.143D-S42.143G,S42.144A,S42.144D-
S42.144G,S42.145A,S42.145D-S42.145G,S42.146A,S42.146D-S42.146G,S42.151A,S42.151D-S42.151G,
S42.152A,S42.152D-S42.152G,S42.153A,S42.153D-S42.153G,S42.154A,S42.154D-S42.154G,S42.155A,
S42.155D-S42.155G,S42.156A,S42.156D-S42.156G,S42.191A,S42.191D-S42.191G,S42.192A,S42.192D-
S42.192G,S42.199A,S42.199D-S42.199G,S42.201A,S42.201D-S42.201G,S42.202A,S42.202D-S42.202G,
S42.209A,S42.209D-S42.209G,S42.211A,S42.211D-S42.211G,S42.212A,S42.212D-S42.212G,S42.213A,
S42.213D-S42.213G,S42.214A,S42.214D-S42.214G,S42.215A,S42.215D-S42.215G,S42.216A,S42.216D-
S42.216G,S42.221A,S42.221D-S42.221G,S42.222A,S42.222D-S42.222G,S42.223A,S42.223D-S42.223G,
S42.224A,S42.224D-S42.224G,S42.225A,S42.225D-S42.225G,S42.226A,S42.226D-S42.226G,S42.231A,
S42.231D-S42.231G,S42.232A,S42.232D-S42.232G,S42.239A,S42.239D-S42.239G,S42.241A,S42.241D-
S42.241G,S42.242A,S42.242D-S42.242G,S42.249A,S42.249D-S42.249G,S42.251A,S42.251D-S42.251G,
S42.252A,S42.252D-S42.252G,S42.253A,S42.253D-S42.253G,S42.254A,S42.254D-S42.254G,S42.255A,
S42.255D-S42.255G,S42.256A,S42.256D-S42.256G,S42.261A,S42.261D-S42.261G,S42.262A,S42.262D-
S42.262G,S42.263A,S42.263D-S42.263G,S42.264A,S42.264D-S42.264G,S42.265A,S42.265D-S42.265G,
S42.266A,S42.266D-S42.266G,S42.271A-S42.271G,S42.272A-S42.272G,S42.279A-S42.279G,S42.291A,
S42.291D-S42.291G,S42.292A,S42.292D-S42.292G,S42.293A,S42.293D-S42.293G,S42.294A,S42.294D-
S42.294G,S42.295A,S42.295D-S42.295G,S42.296A,S42.296D-S42.296G,S42.301A,S42.301D-S42.301G,
S42.302A,S42.302D-S42.302G,S42.309A,S42.309D-S42.309G,S42.311A-S42.311G,S42.312A-S42.312G,
S42.319A-S42.319G,S42.321A,S42.321D-S42.321G,S42.322A,S42.322D-S42.322G,S42.323A,S42.323D-
S42.323G,S42.324A,S42.324D-S42.324G,S42.325A,S42.325D-S42.325G,S42.326A,S42.326D-S42.326G,
S42.331A,S42.331D-S42.331G,S42.332A,S42.332D-S42.332G,S42.333A,S42.333D-S42.333G,S42.334A,
S42.334D-S42.334G,S42.335A,S42.335D-S42.335G,S42.336A,S42.336D-S42.336G,S42.341A,S42.341D-
S42.341G,S42.342A,S42.342D-S42.342G,S42.343A,S42.343D-S42.343G,S42.344A,S42.344D-S42.344G,
S42.345A,S42.345D-S42.345G,S42.346A,S42.346D-S42.346G,S42.351A,S42.351D-S42.351G,S42.352A,
S42.352D-S42.352G,S42.353A,S42.353D-S42.353G,S42.354A,S42.354D-S42.354G,S42.355A,S42.355D-
S42.355G,S42.356A,S42.356D-S42.356G,S42.361A,S42.361D-S42.361G,S42.362A,S42.362D-S42.362G,
S42.363A,S42.363D-S42.363G,S42.364A,S42.364D-S42.364G,S42.365A,S42.365D-S42.365G,S42.366A,
S42.366D-S42.366G,S42.391A,S42.391D-S42.391G,S42.392A,S42.392D-S42.392G,S42.399A,S42.399D-
S42.399G,S42.401A,S42.401D-S42.401G,S42.402A,S42.402D-S42.402G,S42.409A,S42.409D-S42.409G,
S42.411A,S42.411D-S42.411G,S42.412A,S42.412D-S42.412G,S42.413A,S42.413D-S42.413G,S42.414A,
S42.414D-S42.414G,S42.415A,S42.415D-S42.415G,S42.416A,S42.416D-S42.416G,S42.421A,S42.421D-
S42.421G,S42.422A,S42.422D-S42.422G,S42.423A,S42.423D-S42.423G,S42.424A,S42.424D-S42.424G,
S42.425A,S42.425D-S42.425G,S42.426A,S42.426D-S42.426G,S42.431A,S42.431D-S42.431G,S42.432A,
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S82.302D,S82.302G,S82.309A,S82.309D,S82.309G,S82.311A-S82.311G,S82.312A-S82.312G,S82.319A-S82.319G,S82.391A,S82.391D,S82.391G,S82.392A,S82.392D,S82.392G,S82.399A,S82.399D,S82.399G,S82.401A,S82.401D,S82.401G,S82.402A,S82.402D,S82.402G,S82.409A,S82.409D,S82.409G,S82.421A,S82.421D,S82.421G,S82.422A,S82.422D,S82.422G,S82.423A,S82.423D,S82.423G,S82.424A,S82.424D,S82.424G,S82.425A,S82.425D,S82.425G,S82.426A,S82.426D,S82.426G,S82.431A,S82.431D,S82.431G,S82.432A,S82.432D,S82.432G,S82.433A,S82.433D,S82.433G,S82.434A,S82.434D,S82.434G,S82.435A,S82.435D,S82.435G,S82.436A,S82.436D,S82.436G,S82.441A,S82.441D,S82.441G,S82.442A,S82.442D,S82.442G,S82.442J,S82.443A,S82.443D,S82.443G,S82.444A,S82.444D,S82.444G,S82.445A,S82.445D,S82.445G,S82.446A,S82.446D,S82.446G,S82.451A,S82.451D,S82.451G,S82.452A,S82.452D,S82.452G,S82.453A,S82.453D,S82.453G,S82.454A,S82.454D,S82.454G,S82.455A,S82.455D,S82.455G,S82.456A,S82.456D,S82.456G,S82.461A,S82.461D,S82.461G,S82.462A,S82.462D,S82.462G,S82.463A,S82.463D,S82.463G,S82.464A,S82.464D,S82.464G,S82.465A,S82.465D,S82.465G,S82.466A,S82.466D,S82.466G,S82.491A,S82.491D,S82.491G,S82.492A,S82.492D,S82.492G,S82.499A,S82.499D,S82.499G,S82.51XA,S82.51XD,S82.51XG,S82.52XA,S82.52XD,S82.52XG,S82.53XA,S82.53XD,S82.53XG,S82.54XA,S82.54XD,S82.54XG,S82.55XA,S82.55XD,S82.55XG,S82.56XA,S82.56XD,S82.56XG,S82.61XA,S82.61XD,S82.61XG,S82.62XA,S82.62XD,S82.62XG,S82.63XA,S82.63XD,S82.63XG,S82.64XA,S82.64XD,S82.64XG,S82.65XA,S82.65XD,S82.65XG-S82.65XJ,S82.66XA,S82.66XD,S82.66XG,S82.811A-S82.811G,S82.812A-S82.812G,S82.819A-S82.819G,S82.821A-S82.821G,S82.822A-S82.822G,S82.829A-S82.829G,S82.831A,S82.831D,S82.831G,S82.832A,S82.832D,S82.832G,S82.839A,S82.839D,S82.839G,S82.841A,S82.841D,S82.841G,S82.842A,S82.842D,S82.842G,S82.843A,S82.843D,S82.843G,S82.844A,S82.844D,S82.844G,S82.845A,S82.845D,S82.845G,S82.846A,S82.846D,S82.846G,S82.851A,S82.851D,S82.851G,S82.852A,S82.852D,S82.852G,S82.853A,S82.853D,S82.853G,S82.854A,S82.854D,S82.854G,S82.855A,S82.855D,S82.855G,S82.856A,S82.856D,S82.856G,S82.861A,S82.861D,S82.861G,S82.862A,S82.862D,S82.862G,S82.863A,S82.863D,S82.863G,S82.864A,S82.864D,S82.864G,S82.865A,S82.865D,S82.865G,S82.866A,S82.866D,S82.866G,S82.871A,S82.871D,S82.871G,S82.872A,S82.872D,S82.872G,S82.873A,S82.873D,S82.873G,S82.874A,S82.874D,S82.874G,S82.875A,S82.875D,S82.875G,S82.876A,S82.876D,S82.876G,S82.891A,S82.891D,S82.891G,S82.892A,S82.892D,S82.892G,S82.899A,S82.899D,S82.899G,S82.90XA,S82.90XD,S82.90XG,S82.91XA,S82.91XD,S82.91XG,S82.92XA,S82.92XD,S82.92XG,S89.001A-S89.001G,S89.002A-S89.002G,S89.009A-S89.009G,S89.011A-S89.011G,S89.012A-S89.012G,S89.019A-S89.019G,S89.021A-S89.021G,S89.022A-S89.022G,S89.029A-S89.029G,S89.031A-S89.031G,S89.032A-S89.032G,S89.039A-S89.039G,S89.041A-S89.041G,S89.042A-S89.042G,S89.049A-S89.049G,S89.091A-S89.091G,S89.092A-S89.092G,S89.099A-S89.099G,S89.101A-S89.101G,S89.102A-S89.102G,S89.109A-S89.109G,S89.111A-S89.111G,S89.112A-S89.112G,S89.119A-S89.119G,S89.121A-S89.121G,S89.122A-S89.122G,S89.129A-S89.129G,S89.131A-S89.131G,S89.132A-S89.132G,S89.139A-S89.139G,S89.141A-S89.141G,S89.142A-S89.142G,S89.149A-S89.149G,S89.191A-S89.191G,S89.192A-S89.192G,S89.199A-S89.199G,S89.201A-S89.201G,S89.202A-S89.202G,S89.209A-S89.209G,S89.211A-S89.211G,S89.212A-S89.212G,S89.219A-S89.219G,S89.221A-S89.221G,S89.222A-S89.222G,S89.229A-S89.229G,S89.291A-S89.291G,S89.292A-S89.292G,S89.299A-S89.299G,S89.301A-S89.301G,S89.302A-S89.302G,S89.309A-S89.309G,S89.311A-S89.311G,S89.312A-S89.312G,S89.319A-S89.319G,S89.321A-S89.321G,S89.322A-S89.322G,S89.329A-S89.329G,S89.391A-S89.391G,S89.392A-S89.392G,S89.399A-S89.399G,S92.001A,S92.001D-S92.001G,S92.002A,S92.002D-S92.002G,S92.009A,S92.009D-S92.009G,S92.011A,S92.011D-S92.011G,S92.012A,S92.012D-S92.012G,S92.013A,S92.013D-S92.013G,S92.014A,S92.014D-S92.014G,S92.015A,S92.015D-S92.015G,S92.016A,S92.016D-S92.016G,S92.021A,S92.021D-S92.021G,S92.022A,S92.022D-S92.022G,S92.023A,S92.023D-S92.023G,S92.024A,S92.024D-S92.024G,S92.025A,S92.025D-S92.025G,S92.026A,S92.026D-S92.026G,S92.031A,S92.031D-S92.031G,S92.032A,S92.032D-S92.032G,S92.033A,S92.033D-S92.033G,S92.034A,S92.034D-S92.034G,S92.035A,S92.035D-S92.035G,S92.036A,S92.036D-S92.036G,S92.041A,S92.041D-S92.041G,S92.042A,S92.042D-S92.042G,S92.043A,S92.043D-S92.043G,S92.044A,S92.044D-S92.044G,S92.045A,S92.045D-S92.045G,S92.046A,S92.046D-S92.046G,S92.051A,S92.051D-S92.051G,S92.052A,S92.052D-S92.052G,S92.053A,S92.053D-S92.053G,S92.054A,S92.054D-S92.054G,S92.055A,S92.055D-S92.055G,S92.056A,S92.056D-S92.056G,S92.061A,S92.061D-S92.061G,S92.062A,S92.062D-S92.062G,S92.063A,S92.063D-S92.063G,S92.064A,S92.064D-S92.064G,S92.065A,S92.065D-S92.065G,S92.066A,S92.066D-S92.066G,S92.101A,S92.101D-S92.101G,S92.102A,S92.102D-S92.102G,S92.109A,S92.109D-S92.109G,S92.111A,S92.111D-S92.111G,S92.112A,S92.112D-S92.112G,S92.113A,S92.113D-S92.113G,S92.114A,S92.114D-S92.114G,S92.115A,S92.115D-S92.115G,S92.116A,S92.116D-S92.116G,S92.121A,S92.121D-S92.121G,S92.122A,S92.122D-S92.122G,S92.123A,S92.123D-S92.123G,S92.124A,S92.124D-S92.124G,S92.125A,S92.125D-S92.125G,S92.126A,S92.126D-S92.126G,S92.131A,S92.131D-S92.131G,S92.132A,S92.132D-S92.132G,S92.133A,S92.133D-S92.133G,S92.134A,S92.134D-S92.134G,S92.135A,S92.135D-S92.135G,S92.136A,S92.136D-S92.136G,S92.141A,S92.141D-S92.141G,S92.142A,S92.142D-S92.142G,S92.143A,S92.143D-S92.143G,S92.144A,S92.144D-S92.144G,S92.145A,S92.145D-S92.145G,S92.146A,S92.146D-S92.146G,S92.151A,S92.151D-S92.151G,S92.152A,S92.152D-S92.152G,S92.153A,S92.153D-S92.153G,S92.154A,S92.154D-S92.154G,S92.155A,S92.155D-S92.155G,S92.156A,S92.156D-S92.156G,S92.191A,S92.191D-S92.191G,S92.192A,S92.192D-S92.192G,S92.199A,S92.199D-S92.199G,S92.201A,S92.201D-S92.201G,S92.202A,S92.202D-S92.202G,S92.209A,S92.209D-S92.209G,S92.211A,S92.211D-S92.211G,S92.212A,S92.212D-S92.212G,S92.213A,S92.213D-S92.213G,S92.214A,S92.214D-S92.214G,S92.215A,S92.215D-S92.215G,S92.216A,S92.216D-S92.216G,S92.221A,S92.221D-S92.221G,S92.222A,S92.222D-S92.222G,S92.223A,S92.223D-S92.223G,S92.224A,S92.224D-S92.224G,S92.225A,S92.225D-S92.225G,S92.226A,S92.226D-S92.226G,S92.231A,S92.231D-S92.231G,S92.232A,S92.232D-S92.232G,S92.233A,S92.233D-S92.233G,S92.234A,S92.234D-S92.234G,S92.235A,S92.235D-S92.235G,S92.236A,S92.236D-S92.236G,S92.241A,S92.241D-S92.241G,S92.242A,S92.242D-S92.242G,S92.243A,S92.243D-S92.243G,S92.244A,S92.244D-S92.244G,S92.245A,S92.245D-S92.245G,S92.246A,S92.246D-S92.246G,S92.251A,S92.251D-S92.251G,S92.252A,S92.252D-S92.252G,S92.253A,S92.253D-S92.253G,S92.254A,S92.254D-S92.254G,S92.255A,S92.255D-S92.255G,S92.256A,S92.256D-

S92.256G,S92.301A,S92.301D-S92.301G,S92.302A,S92.302D-S92.302G,S92.309A,S92.309D-S92.309G,S92.311A,S92.311D-S92.311G,S92.312A,S92.312D-S92.312G,S92.313A,S92.313D-S92.313G,S92.314A,S92.314D-S92.314G,S92.315A,S92.315D-S92.315G,S92.316A,S92.316D-S92.316G,S92.321A,S92.321D-S92.321G,S92.322A,S92.322D-S92.322G,S92.323A,S92.323D-S92.323G,S92.324A,S92.324D-S92.324G,S92.325A,S92.325D-S92.325G,S92.326A,S92.326D-S92.326G,S92.331A,S92.331D-S92.331G,S92.332A,S92.332D-S92.332G,S92.333A,S92.333D-S92.333G,S92.334A,S92.334D-S92.334G,S92.335A,S92.335D-S92.335G,S92.336A,S92.336D-S92.336G,S92.341A,S92.341D-S92.341G,S92.342A,S92.342D-S92.342G,S92.343A,S92.343D-S92.343G,S92.344A,S92.344D-S92.344G,S92.345A,S92.345D-S92.345G,S92.346A,S92.346D-S92.346G,S92.351A,S92.351D-S92.351G,S92.352A,S92.352D-S92.352G,S92.353A,S92.353D-S92.353G,S92.354A,S92.354D-S92.354G,S92.355A,S92.355D-S92.355G,S92.356A,S92.356D-S92.356G,S92.401A,S92.401D-S92.401G,S92.402A,S92.402D-S92.402G,S92.403A,S92.403D-S92.403G,S92.404A,S92.404D-S92.404G,S92.405A,S92.405D-S92.405G,S92.406A,S92.406D-S92.406G,S92.411A,S92.411D-S92.411G,S92.412A,S92.412D-S92.412G,S92.413A,S92.413D-S92.413G,S92.414A,S92.414D-S92.414G,S92.415A,S92.415D-S92.415G,S92.416A,S92.416D-S92.416G,S92.421A,S92.421D-S92.421G,S92.422A,S92.422D-S92.422G,S92.423A,S92.423D-S92.423G,S92.424A,S92.424D-S92.424G,S92.425A,S92.425D-S92.425G,S92.426A,S92.426D-S92.426G,S92.491A,S92.491D-S92.491G,S92.492A,S92.492D-S92.492G,S92.499A,S92.499D-S92.499G,S92.811A,S92.811D-S92.811G,S92.812A,S92.812D-S92.812G,S92.819A,S92.819D-S92.819G,S92.901A,S92.901D,S92.902A,S92.902D,S92.909A,S92.909D,S99.001A,S99.001D-S99.001G,S99.002A,S99.002D-S99.002G,S99.009A,S99.009D-S99.009G,S99.011A,S99.011D-S99.011G,S99.012A,S99.012D-S99.012G,S99.019A,S99.019D-S99.019G,S99.021A,S99.021D-S99.021G,S99.022A,S99.022D-S99.022G,S99.029A,S99.029D-S99.029G,S99.031A,S99.031D-S99.031G,S99.032A,S99.032D-S99.032G,S99.039A,S99.039D-S99.039G,S99.041A,S99.041D-S99.041G,S99.042A,S99.042D-S99.042G,S99.049A,S99.049D-S99.049G,S99.091A,S99.091D-S99.091G,S99.092A,S99.092D-S99.092G,S99.099A,S99.099D-S99.099G,S99.101A,S99.101D-S99.101G,S99.102A,S99.102D-S99.102G,S99.109A,S99.109D-S99.109G,S99.111A,S99.111D-S99.111G,S99.112A,S99.112D-S99.112G,S99.119A,S99.119D-S99.119G,S99.121A,S99.121D-S99.121G,S99.122A,S99.122D-S99.122G,S99.129A,S99.129D-S99.129G,S99.131A,S99.131D-S99.131G,S99.132A,S99.132D-S99.132G,S99.139A,S99.139D-S99.139G,S99.141A,S99.141D-S99.141G,S99.142A,S99.142D-S99.142G,S99.149A,S99.149D-S99.149G,S99.191A,S99.191D-S99.191G,S99.192A,S99.192D-S99.192G,S99.199A,S99.199D-S99.199G,Z47.2

CPT: 11740,20650,20670-20694,23470,23500-23515,23570-23630,24130,24500-24587,24620,24635,24650-24685,25119,25210-25240,25259,25320,25337-25393,25440-25447,25450-25652,25671,25800-25830,26520,26600-26615,26645-26665,26676,26720-26770,27130,27175-27181,27230-27235,27244,27245,27350,27409,27424,27430,27435,27465-27468,27500-27540,27570,27610,27620,27656,27664,27712,27750-27829,27846,27848,28300,28400-28531,28730,29049-29105,29126-29131,29240,29305-29445,29505,29515,29700-29720,29850-29856,29874-29879,29882,29894,29897-29899,93792,93793,97012,97018,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **356**

Condition: RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE (See Coding Specification Below) (See Guideline Notes 6,15,64,65,71,83,114,158)

Treatment: ARTHROPLASTY/RECONSTRUCTION

ICD-10: L40.50-L40.59,M02.10,M02.111-M02.19,M02.30,M02.311-M02.89,M05.611-M05.9,M06.00,M06.011-M06.29,M06.311-M06.39,M06.80,M06.811-M06.9,M08.00,M08.011-M08.48,M08.811-M08.99,M12.50,M12.511-M12.59,M13.871-M13.879,M16.0,M16.10-M16.9,M17.0,M17.10-M17.9,M18.0,M18.10-M18.9,M19.011-M19.93,M20.20-M20.22,M24.151-M24.176,M24.871-M24.872,M24.874-M24.875,M25.00,M25.011-M25.076,M25.151-M25.159,M25.851-M25.859,M25.871-M25.879,M76.20-M76.22,M87.00,M87.011-M87.9,M90.50,M90.511-M90.59,M93.20,M93.211-M93.29

CPT: 20610,20611,20690-20694,23120,23470-23474,23800,23802,24000,24006,24101,24102,24130,24160,24164,24360-24371,24800,24802,25000,25101-25109,25115-25119,25210-25240,25270,25320,25337,25390-25393,25441-25492,25800,25810-25830,26320,26516-26536,26820-26863,26990-26992,27036,27090,27091,27122-27132,27187,27284,27286,27358,27437-27454,27457,27580,27620-27626,27641,27700-27704,27870,27871,28090,28104,28114,28116,28122,28289-28292,28446,28715,28725,28740,28750,29819-29826,29834-29838,29843-29848,29861-29863,29871-29876,29884-29887,29891,29892,29894-29899,29904-29916,77014,77261-77290,77295,77300,77306,77307,77331-77336,77385-77387,77401-77423,77427,77470,93792,93793,97012,97018,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S2118,S2325

Knee arthroscopy (29871, 29873-29876, 29884-29887) is not included on this line when paired with osteoarthritis/osteoarthrosis of the knee (M17.0-M17.9).

Line: 357
Condition: CONDITIONS OF PULMONARY ARTERY (See Guideline Notes 64,65)
Treatment: SURGICAL TREATMENT
ICD-10: I28.0-I28.9,S25.401A-S25.401D,S25.402A-S25.402D,S25.409A-S25.409D,S25.411A-S25.411D,S25.412A-S25.412D,S25.419A-S25.419D,S25.421A-S25.421D,S25.422A-S25.422D,S25.429A-S25.429D,S25.491A-S25.491D,S25.492A-S25.492D,S25.499A-S25.499D
CPT: 32480-32488,32501,32505-32540,32663,32666-32670,33726,33917-33922,92960-92971,92978-92998,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 358
Condition: BODY INFESTATIONS (E.G., LICE, SCABIES) (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: B83.4,B85.0-B85.4,B86,B87.0-B87.4,B87.81-B87.9,B88.0-B88.9
CPT: 93792,93793,96900,96902,96910-96913,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: 359
Condition: DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS (See Guideline Notes 6,64,65)
Treatment: SURGICAL TREATMENT
ICD-10: M22.00-M22.12,M24.00,M24.011-M24.073,M24.171-M24.176,M24.321-M24.376,M24.411-M24.443,M24.451-M24.476,M24.811-M24.812,M24.821-M24.822,M24.831-M24.832,M24.841-M24.842,M24.851-M24.852,M24.871-M24.872,M24.874-M24.875,M25.871-M25.879,M72.0,M92.40-M92.52,Q66.0-Q66.1,Q66.21-Q66.4,Q66.6-Q66.7,Q68.2,Q69.0-Q69.1,Q70.00-Q70.13,Q71.40-Q71.63,Q71.811-Q71.93,Q72.40-Q72.73,Q72.811-Q72.93,Q73.1-Q73.8,Q74.0,S03.00XA-S03.00XD,S03.01XA-S03.01XD,S03.02XA-S03.02XD,S03.03XA-S03.03XD,S33.30XA-S33.30XD,S33.39XA-S33.39XD,S43.001A-S43.001D,S43.002A-S43.002D,S43.003A-S43.003D,S43.004A-S43.004D,S43.005A-S43.005D,S43.006A-S43.006D,S43.011A-S43.011D,S43.012A-S43.012D,S43.013A-S43.013D,S43.014A-S43.014D,S43.015A-S43.015D,S43.016A-S43.016D,S43.021A-S43.021D,S43.022A-S43.022D,S43.023A-S43.023D,S43.024A-S43.024D,S43.025A-S43.025D,S43.026A-S43.026D,S43.031A-S43.031D,S43.032A-S43.032D,S43.033A-S43.033D,S43.034A-S43.034D,S43.035A-S43.035D,S43.036A-S43.036D,S43.081A-S43.081D,S43.082A-S43.082D,S43.083A-S43.083D,S43.084A-S43.084D,S43.085A-S43.085D,S43.086A-S43.086D,S43.101A-S43.101D,S43.102A-S43.102D,S43.109A-S43.109D,S43.111A-S43.111D,S43.112A-S43.112D,S43.119A-S43.119D,S43.121A-S43.121D,S43.122A-S43.122D,S43.129A-S43.129D,S43.131A-S43.131D,S43.132A-S43.132D,S43.139A-S43.139D,S43.141A-S43.141D,S43.142A-S43.142D,S43.149A-S43.149D,S43.151A-S43.151D,S43.152A-S43.152D,S43.159A-S43.159D,S43.201A-S43.201D,S43.202A-S43.202D,S43.203A-S43.203D,S43.204A-S43.204D,S43.205A-S43.205D,S43.206A-S43.206D,S43.211A-S43.211D,S43.212A-S43.212D,S43.213A-S43.213D,S43.214A-S43.214D,S43.215A-S43.215D,S43.216A-S43.216D,S43.221A-S43.221D,S43.222A-S43.222D,S43.223A-S43.223D,S43.224A-S43.224D,S43.225A-S43.225D,S43.226A-S43.226D,S43.301A-S43.301D,S43.302A-S43.302D,S43.303A-S43.303D,S43.304A-S43.304D,S43.305A-S43.305D,S43.306A-S43.306D,S43.311A-S43.311D,S43.312A-S43.312D,S43.313A-S43.313D,S43.314A-S43.314D,S43.315A-S43.315D,S43.316A-S43.316D,S43.391A-S43.391D,S43.392A-S43.392D,S43.393A-S43.393D,S43.394A-S43.394D,S43.395A-S43.395D,S43.396A-S43.396D,S53.001A-S53.001D,S53.002A-S53.002D,S53.003A-S53.003D,S53.004A-S53.004D,S53.005A-S53.005D,S53.006A-S53.006D,S53.011A-S53.011D,S53.012A-S53.012D,S53.013A-S53.013D,S53.014A-S53.014D,S53.015A-S53.015D,S53.016A-S53.016D,S53.021A-S53.021D,S53.022A-S53.022D,S53.023A-S53.023D,S53.024A-S53.024D,S53.025A-S53.025D,S53.026A-S53.026D,S53.031A-S53.031D,S53.032A-S53.032D,S53.033A-S53.033D,S53.091A-S53.091D,S53.092A-S53.092D,S53.093A-S53.093D,S53.094A-S53.094D,S53.095A-S53.095D,S53.096A-S53.096D,S53.101A-S53.101D,S53.102A-S53.102D,S53.103A-S53.103D,S53.104A-S53.104D,S53.105A-S53.105D,S53.106A-S53.106D,S53.111A-S53.111D,S53.112A-S53.112D,S53.113A-S53.113D,S53.114A-S53.114D,S53.115A-S53.115D,S53.116A-S53.116D,S53.121A-S53.121D,S53.122A-S53.122D,S53.123A-S53.123D,S53.124A-S53.124D,S53.125A-S53.125D,S53.126A-S53.126D,S53.131A-S53.131D,S53.132A-S53.132D,S53.133A-S53.133D,S53.134A-S53.134D,S53.135A-S53.135D,S53.136A-S53.136D,S53.141A-S53.141D,S53.142A-S53.142D,S53.143A-S53.143D,S53.144A-S53.144D,S53.145A-S53.145D,S53.146A-S53.146D,S53.191A-S53.191D,S53.192A-S53.192D,S53.193A-S53.193D,S53.194A-S53.194D,S53.195A-S53.195D,S53.196A-S53.196D,S63.001A-S63.001D,S63.002A-S63.002D,S63.003A-S63.003D,S63.004A-S63.004D,S63.005A-S63.005D,S63.006A-S63.006D,S63.011A-S63.011D,S63.012A-S63.012D,S63.013A-S63.013D,S63.014A-S63.014D,S63.015A-S63.015D,S63.016A-S63.016D,S63.021A-S63.021D,S63.022A-S63.022D,S63.023A-S63.023D,S63.024A-S63.024D,S63.025A-S63.025D,S63.026A-S63.026D,S63.031A-S63.031D,S63.032A-S63.032D,S63.033A-S63.033D,S63.034A-S63.034D,S63.035A-S63.035D,S63.036A-S63.036D,S63.041A-S63.041D,S63.042A-S63.042D,S63.043A-S63.043D,S63.044A-S63.044D,S63.045A-S63.045D,S63.046A-S63.046D,S63.051A-S63.051D,S63.052A-S63.052D,S63.053A-S63.053D,S63.054A-S63.054D,S63.055A-S63.055D,S63.056A-S63.056D,S63.061A-S63.061D,S63.062A-S63.062D,S63.063A-S63.063D,S63.064A-S63.064D,S63.065A-S63.065D,S63.066A-S63.066D,S63.071A-S63.071D,S63.072A-S63.072D,S63.073A-S63.073D,S63.074A-S63.074D,S63.075A-S63.075D,S63.076A-S63.076D,S63.091A-S63.091D,S63.092A-S63.092D,S63.093A-S63.093D,S63.094A-S63.094D,S63.095A-S63.095D,S63.096A-S63.096D,S63.101A-S63.101D,S63.102A-S63.102D,S63.103A-S63.103D,S63.104A-S63.104D,S63.105A-S63.105D,S63.106A-S63.106D,S63.111A-S63.111D,S63.112A-

S63.112D,S63.113A-S63.113D,S63.114A-S63.114D,S63.115A-S63.115D,S63.116A-S63.116D,S63.121A-S63.121D,S63.122A-S63.122D,S63.123A-S63.123D,S63.124A-S63.124D,S63.125A-S63.125D,S63.126A-S63.126D,S63.200A-S63.200D,S63.201A-S63.201D,S63.202A-S63.202D,S63.203A-S63.203D,S63.204A-S63.204D,S63.205A-S63.205D,S63.206A-S63.206D,S63.207A-S63.207D,S63.208A-S63.208D,S63.209A-S63.209D,S63.210A-S63.210D,S63.211A-S63.211D,S63.212A-S63.212D,S63.213A-S63.213D,S63.214A-S63.214D,S63.215A-S63.215D,S63.216A-S63.216D,S63.217A-S63.217D,S63.218A-S63.218D,S63.219A-S63.219D,S63.220A-S63.220D,S63.221A-S63.221D,S63.222A-S63.222D,S63.223A-S63.223D,S63.224A-S63.224D,S63.225A-S63.225D,S63.226A-S63.226D,S63.227A-S63.227D,S63.228A-S63.228D,S63.229A-S63.229D,S63.230A-S63.230D,S63.231A-S63.231D,S63.232A-S63.232D,S63.233A-S63.233D,S63.234A-S63.234D,S63.235A-S63.235D,S63.236A-S63.236D,S63.237A-S63.237D,S63.238A-S63.238D,S63.239A-S63.239D,S63.240A-S63.240D,S63.241A-S63.241D,S63.242A-S63.242D,S63.243A-S63.243D,S63.244A-S63.244D,S63.245A-S63.245D,S63.246A-S63.246D,S63.247A-S63.247D,S63.248A-S63.248D,S63.249A-S63.249D,S63.250A-S63.250D,S63.251A-S63.251D,S63.252A-S63.252D,S63.253A-S63.253D,S63.254A-S63.254D,S63.255A-S63.255D,S63.256A-S63.256D,S63.257A-S63.257D,S63.258A-S63.258D,S63.259A-S63.259D,S63.260A-S63.260D,S63.261A-S63.261D,S63.262A-S63.262D,S63.263A-S63.263D,S63.264A-S63.264D,S63.265A-S63.265D,S63.266A-S63.266D,S63.267A-S63.267D,S63.268A-S63.268D,S63.269A-S63.269D,S63.270A-S63.270D,S63.271A-S63.271D,S63.272A-S63.272D,S63.273A-S63.273D,S63.274A-S63.274D,S63.275A-S63.275D,S63.276A-S63.276D,S63.277A-S63.277D,S63.278A-S63.278D,S63.279A-S63.279D,S63.280A-S63.280D,S63.281A-S63.281D,S63.282A-S63.282D,S63.283A-S63.283D,S63.284A-S63.284D,S63.285A-S63.285D,S63.286A-S63.286D,S63.287A-S63.287D,S63.288A-S63.288D,S63.289A-S63.289D,S63.290A-S63.290D,S63.291A-S63.291D,S63.292A-S63.292D,S63.293A-S63.293D,S63.294A-S63.294D,S63.295A-S63.295D,S63.296A-S63.296D,S63.297A-S63.297D,S63.298A-S63.298D,S63.299A-S63.299D,S73.001A-S73.001D,S73.002A-S73.002D,S73.003A-S73.003D,S73.004A-S73.004D,S73.005A-S73.005D,S73.006A-S73.006D,S73.011A-S73.011D,S73.012A-S73.012D,S73.013A-S73.013D,S73.014A-S73.014D,S73.015A-S73.015D,S73.016A-S73.016D,S73.021A-S73.021D,S73.022A-S73.022D,S73.023A-S73.023D,S73.024A-S73.024D,S73.025A-S73.025D,S73.026A-S73.026D,S73.031A-S73.031D,S73.032A-S73.032D,S73.033A-S73.033D,S73.034A-S73.034D,S73.035A-S73.035D,S73.036A-S73.036D,S73.041A-S73.041D,S73.042A-S73.042D,S73.043A-S73.043D,S73.044A-S73.044D,S73.045A-S73.045D,S73.046A-S73.046D,S83.001A-S83.001D,S83.002A-S83.002D,S83.003A-S83.003D,S83.004A-S83.004D,S83.005A-S83.005D,S83.006A-S83.006D,S83.011A-S83.011D,S83.012A-S83.012D,S83.013A-S83.013D,S83.014A-S83.014D,S83.015A-S83.015D,S83.016A-S83.016D,S83.091A-S83.091D,S83.092A-S83.092D,S83.093A-S83.093D,S83.094A-S83.094D,S83.095A-S83.095D,S83.096A-S83.096D,S83.101A-S83.101D,S83.102A-S83.102D,S83.103A-S83.103D,S83.104A-S83.104D,S83.105A-S83.105D,S83.106A-S83.106D,S83.111A-S83.111D,S83.112A-S83.112D,S83.113A-S83.113D,S83.114A-S83.114D,S83.115A-S83.115D,S83.116A-S83.116D,S83.121A-S83.121D,S83.122A-S83.122D,S83.123A-S83.123D,S83.124A-S83.124D,S83.125A-S83.125D,S83.126A-S83.126D,S83.131A-S83.131D,S83.132A-S83.132D,S83.133A-S83.133D,S83.134A-S83.134D,S83.135A-S83.135D,S83.136A-S83.136D,S83.141A-S83.141D,S83.142A-S83.142D,S83.143A-S83.143D,S83.144A-S83.144D,S83.145A-S83.145D,S83.146A-S83.146D,S83.191A-S83.191D,S83.192A-S83.192D,S83.193A-S83.193D,S83.194A-S83.194D,S83.195A-S83.195D,S83.196A-S83.196D,S93.01XA-S93.01XD,S93.02XA-S93.02XD,S93.03XA-S93.03XD,S93.04XA-S93.04XD,S93.05XA-S93.05XD,S93.06XA-S93.06XD,S93.101A-S93.101D,S93.102A-S93.102D,S93.103A-S93.103D,S93.104A-S93.104D,S93.105A-S93.105D,S93.106A-S93.106D,S93.111A-S93.111D,S93.112A-S93.112D,S93.113A-S93.113D,S93.114A-S93.114D,S93.115A-S93.115D,S93.116A-S93.116D,S93.119A-S93.119D,S93.121A-S93.121D,S93.122A-S93.122D,S93.123A-S93.123D,S93.124A-S93.124D,S93.125A-S93.125D,S93.126A-S93.126D,S93.129A-S93.129D,S93.131A-S93.131D,S93.132A-S93.132D,S93.133A-S93.133D,S93.134A-S93.134D,S93.135A-S93.135D,S93.136A-S93.136D,S93.139A-S93.139D,S93.141A-S93.141D,S93.142A-S93.142D,S93.143A-S93.143D,S93.144A-S93.144D,S93.145A-S93.145D,S93.146A-S93.146D,S93.149A-S93.149D,S93.301A-S93.301D,S93.302A-S93.302D,S93.303A-S93.303D,S93.304A-S93.304D,S93.305A-S93.305D,S93.306A-S93.306D,S93.311A-S93.311D,S93.312A-S93.312D,S93.313A-S93.313D,S93.314A-S93.314D,S93.315A-S93.315D,S93.316A-S93.316D,S93.321A-S93.321D,S93.322A-S93.322D,S93.323A-S93.323D,S93.324A-S93.324D,S93.325A-S93.325D,S93.326A-S93.326D,S93.331A-S93.331D,S93.332A-S93.332D,S93.333A-S93.333D,S93.334A-S93.334D,S93.335A-S93.335D,S93.336A-S93.336D,Z47.1

CPT: 11200,20527,20690-20694,21480,23455,23462-23470,23520-23552,23650-23700,24000,24006,24101,24102,24300,24332,24343,24345,24346,24600-24640,25001,25101-25109,25259,25275,25320,25335,25337,25390-25394,25430,25431,25441-25445,25447,25450-25492,25660-25695,25810-25830,26035,26040,26060,26121-26180,26320-26341,26390,26440-26596,26641-26715,26770-26863,26951,27033,27097,27100-27122,27138-27170,27179,27185,27250-27258,27265,27266,27269,27275,27306,27307,27350,27420-27495,27550-27598,27603-27612,27615,27618-27630,27634-27692,27698,27705,27715,27727-27742,27829-27860,28008-28035,28043-28072,28086-28092,28110-28118,28126-28160,28220-28280,28288,28300-28305,28307-28341,28360,28540-28730,28737-28760,29049-29105,29126-29131,29305-29515,29700-29720,29750,29806-29819,29822,29823,29828,29834,29861-29863,29873,29874,29881,29882,29891,29892,29894,29904-29907,64702,64704,93792,93793,97012,97018,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: D7810-D7830,G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2115

Line: **360**
Condition: CHORIORETINAL INFLAMMATION (See Guideline Notes 10,64,65,116)
Treatment: MEDICAL, SURGICAL, AND LASER TREATMENT
ICD-10: A50.01,A50.30,A50.39,A51.43,A52.71,B58.00,B58.09,H20.821-H20.829,H30.001-H30.93,H31.21,H32,H44.111-H44.119,H44.131-H44.139
CPT: 67027,67028,67036-67043,67208,67210,67220,67227-67229,67515,92002-92014,92018-92060,92081-92136,92225-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **361**
Condition: SCOLIOSIS (See Guideline Notes 41,56,60,64,65,92,100)
Treatment: MEDICAL AND SURGICAL THERAPY
ICD-10: M41.00-M41.08,M41.112-M41.9,M96.5,Q67.5,Q76.3,Z47.82
CPT: 20660-20665,20930-20938,21720,21725,22206-22226,22532-22855,22859,29000-29046,29710,29720,62287,63001-63091,63170,63180-63199,63295-63610,63650,63655,63685,93792,93793,96150-96155,97110-97124,97140-97168,97530,97535,97760,97763,97810-98942,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487,99489,99495,99496,99605-99607
HCPCS: G0157-G0160,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0508-G0511,G0513,G0514

Line: **362**
Condition: DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM (See Coding Specification Below) (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: G10,G21.0,G23.0-G23.9,G24.02-G24.3,G24.5-G24.9,G25.0-G25.5,G25.61-G25.69,G25.9,G80.3,G90.3,J38.5
CPT: 31513,31570,31571,31573,31641,64612,64616,93792,93793,95873,95874,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Chemodenervation with botulinum toxin injection (CPT 64612, 64616) is included on this line only for treatment of blepharospasm (ICD-10-CM G24.5), spasmodic torticollis (ICD-10-CM G24.3), and other fragments of torsion dystonia (ICD-10-CM G24.9)

Line: **363**
Condition: CYST AND PSEUDOCYST OF PANCREAS (See Guideline Notes 64,65)
Treatment: DRAINAGE OF PANCREATIC CYST
ICD-10: K86.2-K86.3
CPT: 43240,43274-43276,48000-48020,48105-48148,48152-48154,48500-48540,48548,49322,49324,49325,49405,49421-49423,64680,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **364**
Condition: ACUTE SINUSITIS (See Guideline Notes 64,65)
Treatment: MEDICAL TREATMENT
ICD-10: J01.00,J01.10,J01.20,J01.30,J01.40,J01.80,J01.90
CPT: 31000,31002,31090,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514,S2342

Line: **365**
Condition: HYPHEMA
Treatment: REMOVAL OF BLOOD CLOT
ICD-10: H21.00-H21.03
CPT: 65810,65815,65930,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: 366
Condition: ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: B44.81
CPT: 32662,33405-33430,33973,33974,35180-35184,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 367
Condition: ENTROPION AND TRICHIASIS OF EYELID
Treatment: REPAIR
ICD-10: H02.001-H02.059
CPT: 67820-67850,67880,67882,67921-67924,67950-67975,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: 368
Condition: STREPTOCOCCAL SORE THROAT AND SCARLET FEVER; VINCENT'S DISEASE; ULCER OF TONSIL; UNILATERAL HYPERTROPHY OF TONSIL (See Guideline Notes 36,64,65)
Treatment: MEDICAL THERAPY, TONSILLECTOMY/ADENOIDECTOMY
ICD-10: A38.0-A38.9,A69.0-A69.1,J02.0,J03.00-J03.01,J35.1,J35.3-J35.8
CPT: 42820-42826,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 369
Condition: INTESTINAL PARASITES (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A07.2-A07.4,A07.9,B65.0-B65.9,B66.0-B66.9,B67.0-B67.2,B67.31-B67.99,B68.0,B72,B73.00-B73.1,B74.0-B74.9,B76.0-B76.9,B77.0,B77.81-B77.9,B78.0,B78.7-B78.9,B79-B80,B81.0-B81.8,B82.0-B82.9,B83.0-B83.3,B83.8-B83.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 370
Condition: AMBLYOPIA (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: H53.001-H53.039
CPT: 65778-65782,66820-66986,67311-67343,67901-67909,68135,68320-68328,68335,68340,68371,92002-92014,92018-92060,92081-92136,92225,92226,92230-92310,92314,92325-92342,92370,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 371
Condition: ENCEPHALOCELE
Treatment: SURGICAL TREATMENT
ICD-10: Q01.0-Q01.9
CPT: 20664,61020,61070,61107,61210,61215,61322,61323,62100,62120,62121,62160-62163,62180-62258,62272,63740-63746,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 372
Condition: BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS (See Guideline Notes 12,16,64,65)
Treatment: LOBECTOMY, MEDICAL THERAPY, WHICH INCLUDES RADIATION THERAPY
ICD-10: D14.1-D14.2,D14.30-D14.4,D15.0-D15.9,D19.0,D3A.090-D3A.091,G89.3,Z51.0
CPT: 19260-19272,21627,21630,31512,31541-31546,31572,31592,31630,31631,31636-31641,31770,31775,32320,32480-32488,32505-32540,32553,32661-32663,32666-32670,32673,33120,33130,39000,39010,39220,49411,60520-60522,77014,77261-77290,77295,77306-77318,77331-77370,77385-77387,77402-77432,77469,77470,77600-77763,77770-77790,79005-79445,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017

Line: **373**
Condition: ACNE CONGLOBATA (SEVERE CYSTIC ACNE) (See Guideline Notes 64,65,132)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: L70.0-L70.9,L73.0
CPT: 10040-10061,11900,11901,17000,17340,17360,93792,93793,96900,96902,96910-96913,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **374**
Condition: RETINAL TEAR (See Guideline Notes 64,65,171)
Treatment: LASER PROPHYLAXIS
ICD-10: H33.301-H33.339,H35.411-H35.419
CPT: 67039,67141,67145,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **375**
Condition: CHOLESTEATOMA; INFECTIONS OF THE PINNA (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: H60.40-H60.43,H61.001-H61.039,H70.811-H70.899,H71.00-H71.93,H74.11-H74.23,H74.311-H74.399,H95.00-H95.03,H95.121-H95.129
CPT: 21235,69220,69420,69421,69433-69540,69601-69646,69662,69670,69700,69905,69910,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **376**
Condition: DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT (See Guideline Notes 6,28,64,65,98,120)
Treatment: REPAIR
ICD-10: M12.00,M12.011-M12.09,M25.751-M25.759,M35.4,M62.10,M62.111-M62.28,M62.89,M65.311-M65.319,M66.0,M66.111-M66.18,M66.221-M66.259,M66.271-M66.80,M66.821-M66.89,M70.60-M70.72,M72.8,M76.00-M76.12,M76.30-M76.32,S53.20XA-S53.20XD,S53.21XA-S53.21XD,S53.22XA-S53.22XD,S53.30XA-S53.30XD,S53.31XA-S53.31XD,S53.32XA-S53.32XD,S53.401A-S53.401D,S53.402A-S53.402D,S53.409A-S53.409D,S53.411A-S53.411D,S53.412A-S53.412D,S53.419A-S53.419D,S53.421A-S53.421D,S53.422A-S53.422D,S53.429A-S53.429D,S53.431A-S53.431D,S53.432A-S53.432D,S53.439A-S53.439D,S53.441A-S53.441D,S53.442A-S53.442D,S53.449A-S53.449D,S53.491A-S53.491D,S53.492A-S53.492D,S53.499A-S53.499D,S56.011A-S56.011D,S56.012A-S56.012D,S56.019A-S56.019D,S56.111A-S56.111D,S56.112A-S56.112D,S56.113A-S56.113D,S56.114A-S56.114D,S56.115A-S56.115D,S56.116A-S56.116D,S56.117A-S56.117D,S56.118A-S56.118D,S56.119A-S56.119D,S56.211A-S56.211D,S56.212A-S56.212D,S56.219A-S56.219D,S56.311A-S56.311D,S56.312A-S56.312D,S56.319A-S56.319D,S56.411A-S56.411D,S56.412A-S56.412D,S56.413A-S56.413D,S56.414A-S56.414D,S56.415A-S56.415D,S56.416A-S56.416D,S56.417A-S56.417D,S56.418A-S56.418D,S56.419A-S56.419D,S56.511A-S56.511D,S56.512A-S56.512D,S56.519A-S56.519D,S56.811A-S56.811D,S56.812A-S56.812D,S56.819A-S56.819D,S56.911A-S56.911D,S56.912A-S56.912D,S56.919A-S56.919D,S63.301A-S63.301D,S63.302A-S63.302D,S63.309A-S63.309D,S63.311A-S63.311D,S63.312A-S63.312D,S63.319A-S63.319D,S63.321A-S63.321D,S63.322A-S63.322D,S63.329A-S63.329D,S63.331A-S63.331D,S63.332A-S63.332D,S63.339A-S63.339D,S63.391A-S63.391D,S63.392A-S63.392D,S63.399A-S63.399D,S63.400A-S63.400D,S63.401A-S63.401D,S63.402A-S63.402D,S63.403A-S63.403D,S63.404A-S63.404D,S63.405A-S63.405D,S63.406A-S63.406D,S63.407A-S63.407D,S63.408A-S63.408D,S63.409A-S63.409D,S63.410A-S63.410D,S63.411A-S63.411D,S63.412A-S63.412D,S63.413A-S63.413D,S63.414A-S63.414D,S63.415A-S63.415D,S63.416A-S63.416D,S63.417A-S63.417D,S63.418A-S63.418D,S63.419A-S63.419D,S63.420A-S63.420D,S63.421A-S63.421D,S63.422A-S63.422D,S63.423A-S63.423D,S63.424A-S63.424D,S63.425A-S63.425D,S63.426A-S63.426D,S63.427A-S63.427D,S63.428A-S63.428D,S63.429A-S63.429D,S63.430A-S63.430D,S63.431A-S63.431D,S63.432A-S63.432D,S63.433A-S63.433D,S63.434A-S63.434D,S63.435A-S63.435D,S63.436A-S63.436D,S63.437A-S63.437D,S63.438A-S63.438D,S63.439A-S63.439D,S63.490A-S63.490D,S63.491A-S63.491D,S63.492A-S63.492D,S63.493A-S63.493D,S63.494A-S63.494D,S63.495A-S63.495D,S63.496A-S63.496D,S63.497A-S63.497D,S63.498A-S63.498D,S63.499A-S63.499D,S63.501A-S63.501D,S63.502A-S63.502D,S63.509A-S63.509D,S63.511A-S63.511D,S63.512A-S63.512D,S63.519A-S63.519D,S63.521A-S63.521D,S63.522A-S63.522D,S63.529A-S63.529D,S63.591A-S63.591D,S63.592A-S63.592D,S63.599A-S63.599D,S63.601A-S63.601D,S63.602A-S63.602D,S63.609A-S63.609D,S63.610A-S63.610D,S63.611A-S63.611D,S63.612A-S63.612D,S63.613A-S63.613D,S63.614A-S63.614D,S63.615A-S63.615D,S63.616A-S63.616D,S63.617A-S63.617D,S63.618A-S63.618D,S63.619A-S63.619D,S63.621A-S63.621D,S63.622A-S63.622D,S63.629A-S63.629D,S63.630A-S63.630D,S63.631A-S63.631D,S63.632A-S63.632D,S63.633A-S63.633D,S63.634A-S63.634D,S63.635A-S63.635D,S63.636A-S63.636D,S63.637A-S63.637D,S63.638A-S63.638D,S63.639A-S63.639D,S63.641A-S63.641D,S63.642A-S63.642D,S63.649A-S63.649D,S63.650A-S63.650D,S63.651A-S63.651D,S63.652A-S63.652D,S63.653A-S63.653D,S63.654A-S63.654D,S63.655A-S63.655D,S63.656A-S63.656D,S63.657A-S63.657D,S63.658A-S63.658D,S63.659A-S63.659D,S63.681A-S63.681D,S63.682A-S63.682D,S63.689A-S63.689D,S63.690A-

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CPT: 20550,20610,20611,23430,24340-24342,24344,25310,26055,26350-26412,26418,26420,26428-26437,26474,26480,26497,26530,26540,26775,26776,27380-27386,27650-27654,27658-27675,27695-27698,27829,28200-28210,29065-29105,29126-29280,29345-29425,29440,29445,29505-29540,29700,29705,29828,29861-29863,29901,29902,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **377**

Condition: DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION (See Guideline Notes 6,38,64,65,90)

Treatment: MEDICAL THERAPY (SHORT TERM REHABILITATION WITH DEFINED GOALS)

ICD-10: A33,A50.40,A50.43,A50.45,A52.10-A52.19,A52.3,A81.00-A81.83,A87.1-A87.2,A88.8,A89,C70.0-C70.9,C71.0-C71.9,C72.0-C72.1,C72.20-C72.9,D33.9,D81.3,D81.5,E00.0-E00.9,E45,E70.0-E70.1,E70.20-E70.29,E70.320-E70.331,E70.39,E70.5-E70.9,E71.0,E71.110-E71.548,E72.00-E72.51,E72.59-E72.9,E74.00-E74.09,E74.20-E74.29,E75.00-E75.09,E75.11-E75.23,E75.240-E75.6,E76.01-E76.1,E76.210-E76.9,E77.0-E77.9,E78.70-E78.9,E79.1-E79.9,E80.0-E80.1,E80.20-E80.3,E83.00-E83.09,E88.2,E88.40-E88.49,E88.89,F01.50-F01.51,F03.90-F03.91,F06.1,F06.8,F07.89,F70-F79,F84.0-F84.3,F84.8,G04.1,G04.81-G04.91,G10,G11.0-G11.9,G12.0-G12.1,G12.21-G12.9,G13.1-G13.8,G14-G20,G21.0,G21.11-G21.9,G23.0-G23.9,G24.01,G24.1-G24.2,G24.8,G25.4-G25.5,G25.82,G25.9,G30.0-G30.8,G31.01-G31.9,G32.0,G32.81-G32.89,G35,G36.0-G36.9,G37.0-G37.9,G40.011-G40.019,G40.111-G40.119,G40.211-G40.219,G40.311-G40.319,G40.411-G40.419,G40.811,G40.89,G40.911-G40.919,G60.0-G60.8,G61.0-G61.1,G61.81-G61.89,G62.0-G62.2,G62.81-G62.89,G64,G71.0,G71.11-G71.8,G72.0-G72.3,G72.41-G72.89,G73.7,G80.0-G80.9,G81.00-G81.94,G82.20-G82.54,G83.0,G83.10-G83.9,G90.01-G90.1,G90.3-G90.4,G90.50,G90.511-G90.59,G91.0-G91.9,G92,G93.0-G93.1,G93.40-G93.81,G93.89,G94,G95.0,G95.11-G95.89,G97.0,G97.2,G97.31-G97.32,G97.48-G97.49,G97.61-G97.82,G98.0,G99.0-G99.8,H49.811-H49.819,H54.0X33-H54.3,H54.8,I61.0-I61.9,I62.00-I62.9,I63.30,I63.311-I63.312,I63.319-I63.322,I63.329-I63.332,I63.339-I63.342,I63.349-I63.412,I63.419-I63.422,I63.429-I63.432,I63.439-I63.442,I63.449-I63.512,I63.519-I63.522,I63.529-I63.532,I63.539-I63.542,I63.549-I63.9,I67.3,I67.81-I67.83,I67.841-I67.89,I69.010-I69.018,I69.020-I69.090,I69.092-I69.093,I69.110-I69.118,I69.120-I69.190,I69.192-I69.193,I69.210-I69.218,I69.220-I69.290,I69.292-I69.293,I69.310-I69.318,I69.320-I69.390,I69.392-I69.393,I69.810-I69.818,I69.820-I69.890,I69.892-I69.893,I69.910-I69.918,I69.920-I69.990,I69.992-I69.993,I97.810-I97.821,M14.60,M14.611-M14.69,M20.021-M20.099,M21.00,M21.021-M21.079,M21.121-M21.172,M21.20,M21.211-M21.379,M21.511-M21.529,M21.541-M21.549,M21.6X1-M21.969,M61.111-M61.112,M61.121-M61.122,M61.131-M61.132,M61.141-M61.142,M61.144-M61.145,M61.151-M61.152,M61.161-M61.162,M61.171-M61.172,M61.174-M61.175,M61.177-M61.178,M61.18-M61.19,M61.211-M61.212,M61.221-M61.222,M61.231-M61.232,M61.241-M61.242,M61.251-M61.252,M61.261-M61.262,M61.271-M61.272,M61.28-M61.29,M61.311-M61.312,M61.321-M61.322,M61.331-M61.332,M61.341-M61.342,M61.351-M61.352,M61.361-M61.362,M61.371-M61.372,M61.38-M61.39,M61.411-M61.412,M61.421-M61.422,M61.431-M61.432,M61.441-M61.442,M61.451-M61.452,M61.461-M61.462,M61.471-M61.472,M61.48-M61.49,M61.511-M61.512,M61.521-M61.522,M61.531-M61.532,M61.541-M61.542,M61.551-M61.552,M61.561-M61.562,M61.571-M61.572,M61.58-M61.59,M62.3,M62.511-M62.59,M62.89,P07.00-P07.39,P10.0-P10.9,P11.0,P11.2,P11.5-P11.9,P19.0-P19.9,P24.00-P24.21,P24.80-P24.9,P35.0-P35.9,P37.0-P37.9,P39.2,P50.0-P50.9,P51.0-P51.9,P52.0-P52.1,P52.21-P52.9,P54.1-P54.9,P55.1-P55.9,P56.0,P56.90-P56.99,P57.0,P91.2,P91.60-P91.63,P96.81,Q00.0-Q00.2,Q01.0-Q01.9,Q02,Q03.0-Q03.9,Q04.0-Q04.9,Q05.0-Q05.9,Q06.0-Q06.9,Q07.00-Q07.9,Q68.1,Q71.00-Q71.33,Q72.00-Q72.33,Q73.0,Q74.3,Q77.3,Q77.6,Q78.0-Q78.3,Q78.5-Q78.6,Q85.1,Q86.0-Q86.8,Q87.1-Q87.3,Q87.40,Q87.410-Q87.89,Q89.4-Q89.8,Q90.0-Q90.9,Q91.0-Q91.7,Q92.0-

Q92.5,Q92.62-Q92.9,Q93.0-Q93.7,Q93.81-Q93.9,Q95.2-Q95.8,Q96.0-Q96.9,Q97.0-Q97.8,Q98.0-Q98.3,Q98.5-Q98.8,Q99.0-Q99.8,R41.4,R41.81,R53.2,R54,S06.370A-S06.370D,S06.810A-S06.810D,S06.811A-S06.811D,S06.812A-S06.812D,S06.813A-S06.813D,S06.814A-S06.814D,S06.815A-S06.815D,S06.816A-S06.816D,S06.817A-S06.819D,S06.820A-S06.820D,S06.821A-S06.821D,S06.822A-S06.822D,S06.823A-S06.823D,S06.824A-S06.824D,S06.825A-S06.825D,S06.826A-S06.826D,S06.827A-S06.829D,S06.890A-S06.890D,S06.891A-S06.891D,S06.892A-S06.892D,S06.893A-S06.893D,S06.894A-S06.894D,S06.895A-S06.895D,S06.896A-S06.896D,S06.897A-S06.899D,S06.9X0A-S06.9X0D,S06.9X1A-S06.9X1D,S06.9X2A-S06.9X2D,S06.9X3A-S06.9X3D,S06.9X4A-S06.9X4D,S06.9X5A-S06.9X5D,S06.9X6A-S06.9X6D,S06.9X7A-S06.9X9D,S14.0XXA-S14.0XXD,S14.101A-S14.101D,S14.102A-S14.102D,S14.103A-S14.103D,S14.104A-S14.104D,S14.105A-S14.105D,S14.106A-S14.106D,S14.107A-S14.107D,S14.108A-S14.108D,S14.109A-S14.109D,S14.111A-S14.111D,S14.112A-S14.112D,S14.113A-S14.113D,S14.114A-S14.114D,S14.115A-S14.115D,S14.116A-S14.116D,S14.117A-S14.117D,S14.118A-S14.118D,S14.119A-S14.119D,S14.121A-S14.121D,S14.122A-S14.122D,S14.123A-S14.123D,S14.124A-S14.124D,S14.125A-S14.125D,S14.126A-S14.126D,S14.127A-S14.127D,S14.128A-S14.128D,S14.129A-S14.129D,S14.131A-S14.131D,S14.132A-S14.132D,S14.133A-S14.133D,S14.134A-S14.134D,S14.135A-S14.135D,S14.136A-S14.136D,S14.137A-S14.137D,S14.138A-S14.138D,S14.139A-S14.139D,S14.141A-S14.141D,S14.142A-S14.142D,S14.143A-S14.143D,S14.144A-S14.144D,S14.145A-S14.145D,S14.146A-S14.146D,S14.147A-S14.147D,S14.148A-S14.148D,S14.149A-S14.149D,S14.151A-S14.151D,S14.152A-S14.152D,S14.153A-S14.153D,S14.154A-S14.154D,S14.155A-S14.155D,S14.156A-S14.156D,S14.157A-S14.157D,S14.158A-S14.158D,S14.159A-S14.159D,S14.2XXA-S14.2XXD,S14.3XXA-S14.3XXD,S24.0XXA-S24.0XXD,S24.101A-S24.101D,S24.102A-S24.102D,S24.103A-S24.103D,S24.104A-S24.104D,S24.109A-S24.109D,S24.111A-S24.111D,S24.112A-S24.112D,S24.113A-S24.113D,S24.114A-S24.114D,S24.119A-S24.119D,S24.131A-S24.131D,S24.132A-S24.132D,S24.133A-S24.133D,S24.134A-S24.134D,S24.139A-S24.139D,S24.141A-S24.141D,S24.142A-S24.142D,S24.143A-S24.143D,S24.144A-S24.144D,S24.149A-S24.149D,S24.151A-S24.151D,S24.152A-S24.152D,S24.153A-S24.153D,S24.154A-S24.154D,S24.159A-S24.159D,S24.2XXA-S24.2XXD,S34.01XA-S34.01XD,S34.02XA-S34.02XD,S34.101A-S34.101D,S34.102A-S34.102D,S34.103A-S34.103D,S34.104A-S34.104D,S34.105A-S34.105D,S34.109A-S34.109D,S34.111A-S34.111D,S34.112A-S34.112D,S34.113A-S34.113D,S34.114A-S34.114D,S34.115A-S34.115D,S34.119A-S34.119D,S34.121A-S34.121D,S34.122A-S34.122D,S34.123A-S34.123D,S34.124A-S34.124D,S34.125A-S34.125D,S34.129A-S34.129D,S34.131A-S34.131D,S34.132A-S34.132D,S34.139A-S34.139D,S34.21XA-S34.21XD,S34.22XA-S34.22XD,S34.3XXA-S34.3XXD,S34.4XXA-S34.4XXD,T40.0X1A-T40.0X1D,T40.0X2A-T40.0X2D,T40.0X3A-T40.0X3D,T40.0X4A-T40.0X4D,T40.1X1A-T40.1X1D,T40.1X2A-T40.1X2D,T40.1X3A-T40.1X3D,T40.1X4A-T40.1X4D,T40.2X1A-T40.2X1D,T40.2X2A-T40.2X2D,T40.2X3A-T40.2X3D,T40.2X4A-T40.2X4D,T40.3X1A-T40.3X1D,T40.3X2A-T40.3X2D,T40.3X3A-T40.3X3D,T40.3X4A-T40.3X4D,T40.4X1A-T40.4X1D,T40.4X2A-T40.4X2D,T40.4X3A-T40.4X3D,T40.4X4A-T40.4X4D,T40.5X1A-T40.5X1D,T40.5X2A-T40.5X2D,T40.5X3A-T40.5X3D,T40.5X4A-T40.5X4D,T40.601A-T40.601D,T40.602A-T40.602D,T40.603A-T40.603D,T40.604A-T40.604D,T40.691A-T40.691D,T40.692A-T40.692D,T40.693A-T40.693D,T40.694A-T40.694D,T40.7X1A-T40.7X1D,T40.7X2A-T40.7X2D,T40.7X3A-T40.7X3D,T40.7X4A-T40.7X4D,T40.8X1A-T40.8X1D,T40.8X2A-T40.8X2D,T40.8X3A-T40.8X3D,T40.8X4A-T40.8X4D,T40.901A-T40.901D,T40.902A-T40.902D,T40.903A-T40.903D,T40.904A-T40.904D,T40.991A-T40.991D,T71.111A-T71.111D,T71.112A-T71.112D,T71.113A-T71.113D,T71.114A-T71.114D,T71.121A-T71.121D,T71.122A-T71.122D,T71.123A-T71.123D,T71.124A-T71.124D,T71.131A-T71.131D,T71.132A-T71.132D,T71.133A-T71.133D,T71.134A-T71.134D,T71.141A-T71.141D,T71.143A-T71.143D,T71.144A-T71.144D,T71.151A-T71.151D,T71.152A-T71.152D,T71.153A-T71.153D,T71.154A-T71.154D,T71.161A-T71.161D,T71.162A-T71.162D,T71.163A-T71.163D,T71.164A-T71.164D,T71.191A-T71.191D,T71.192A-T71.192D,T71.193A-T71.193D,T71.194A-T71.194D,T71.20XA-T71.20XD,T71.21XA-T71.21XD,T71.221A-T71.221D,T71.222A-T71.222D,T71.223A-T71.223D,T71.224A-T71.224D,T71.231A-T71.231D,T71.232A-T71.232D,T71.233A-T71.233D,T71.234A-T71.234D,T71.29XA-T71.29XD,T71.9XXA-T71.9XXD,T74.4XXA-T74.4XXD,T75.01XA-T75.01XD,T75.09XA-T75.09XD,T75.1XXA-T75.1XXD,T75.4XXA-T75.4XXD,T78.00XA-T78.00XD,T78.01XA-T78.01XD,T78.02XA-T78.02XD,T78.03XA-T78.03XD,T78.04XA-T78.04XD,T78.05XA-T78.05XD,T78.06XA-T78.06XD,T78.07XA-T78.07XD,T78.08XA-T78.08XD,T78.09XA-T78.09XD,T78.3XXA-T78.3XXD,T78.8XXA-T78.8XXD,T79.0XXA-T79.0XXD,T79.4XXA-T79.4XXD,T79.6XXA-T79.6XXD,T88.2XXA-T88.2XXD,T88.51XA-T88.51XD,T88.6XXA-T88.6XXD,Z44.001-Z44.22,Z44.8,Z46.3,Z46.89,Z47.81,Z87.820,Z89.011-Z89.9,Z90.01

CPT: 61215,92002-92014,92083,93792,93793,96150-96155,97012,97110-97127,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513-G0515,S2117

Line: 378
Condition: ESOPHAGEAL STRICTURE; ACHALASIA (See Coding Specification Below) (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: K20.0,K22.0,K22.2,Z46.59
CPT: 32110-32124,32820,43192,43195,43196,43201,43212-43214,43220,43226,43229,43233,43248,43249,43266,43279,43330,43410-43453,44300,49442,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Chemodenervation with botulinum toxin injection (CPT 43201) is included on this line for treatment of achalasia (ICD-10 K22.0)

Line: **379**
Condition: CHRONIC ULCER OF SKIN (See Guideline Notes 62,64,65,163)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: E08.621-E08.622,E09.621-E09.622,E10.621-E10.622,E11.621-E11.622,E13.621-E13.622,I70.231-I70.25,I70.331-I70.35,I70.431-I70.45,I70.531-I70.55,I70.631-I70.65,I70.731-I70.75,I83.001-I83.029,I83.201-I83.229,I87.011-I87.019,I87.031-I87.039,I87.311-I87.319,I87.331-I87.339,L88,L89.000-L89.95,L97.101-L97.929,L98.411-L98.499
CPT: 10060,10061,11000-11047,13101,13102,14350-15005,15271-15278,15920-15958,27598,27880,27881,27884-27888,28120,28122,28800-28825,29445,29580-29584,36465,36466,36470-36479,37700-37785,93792,93793,96150-96155,97605-97608,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: D7920,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **380**
Condition: ESOPHAGITIS; GERD (See Guideline Note 144)
Treatment: SHORT-TERM MEDICAL THERAPY; SURGICAL TREATMENT
ICD-10: K20.8-K20.9,K21.0-K21.9,K22.5,K22.70,K22.710
CPT: 43030,43130-43180,43192,43201,43210,43227,43279-43282,43327-43337,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **381**
Condition: BULIMIA NERVOSA AND UNSPECIFIED EATING DISORDERS (See Coding Specification Below) (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F50.2,F50.81,F50.89-F50.9
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,97802-97804,98966-98969,99051,99060,99201-99239,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005

ICD-10 F50.89 is included on Line 381 for psychogenic loss of appetite. ICD-10 F50.89 is included on Line 629 for pica in adults and for all other diagnoses using this code.

Line: **382**
Condition: LATE SYPHILIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A52.10-A52.15,A52.19-A52.9,A53.0-A53.9
CPT: 47015,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **383**
Condition: CENTRAL SEROUS CHORIORETINOPATHY (See Coding Specification Below) (See Guideline Notes 10,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: H31.401-H31.8,H35.50-H35.54,H35.711-H35.719,H44.421-H44.429
CPT: 66020,67005-67028,67036-67043,67210,67515,68200,92002-92014,92018-92060,92081-92100,92134,92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

CPT 67027 (Implantation of intravitreal drug delivery system) is included on this line for use with medications other than intraocular steroid implants.

Line: **384**
Condition: DENTAL CONDITIONS (E.G., PULPAL PATHOLOGY, PERMANENT ANTERIOR TOOTH)
Treatment: BASIC ENDODONTICS (I.E., ROOT CANAL THERAPY)
HCPCS: D3310,D3332

Line: **385**
Condition: SUPERFICIAL INJURIES WITH INFECTION (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: L08.89-L08.9,T79.8XXA-T79.8XXD
CPT: 10120-10160,11000,11001,12001-12014,28190,29515,93792,93793,98966-98969,99051,99060,99070,99078, 99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **386**
Condition: PITUITARY DWARFISM (See Guideline Notes 64,65,74)
Treatment: MEDICAL THERAPY
ICD-10: E23.0,Q77.0-Q77.1,Q77.4-Q77.5,Q77.7-Q77.8
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, S9558

Line: **387**
Condition: ANOGENITAL VIRAL WARTS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: A63.0
CPT: 11420-11426,17000-17004,46900-46924,54050-54065,56501,56515,57061,57065,57150,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **388**
Condition: SEPARATION ANXIETY DISORDER (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F93.0
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224, 99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004, H0019,H0023,H0032-H0038,H0045,H2010,H2012-H2014,H2021,H2022,H2027,H2032,H2033,S9484,T1005

Line: **389**
Condition: ACUTE OTITIS MEDIA (See Guideline Notes 29,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: H65.00-H65.07,H65.111-H65.199,H66.001-H66.019,H66.40-H66.93,H67.1-H67.9,H68.011-H68.019,H69.90-H69.93,H73.001-H73.099,H73.20-H73.23,T70.0XXA-T70.0XXD
CPT: 69209,69210,69420,69421,69433,69436,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215, 99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **390**
Condition: INTESTINAL DISACCHARIDASE AND OTHER DEFICIENCIES (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: E72.52-E72.53,E74.10,E74.31-E74.39
CPT: 93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **391**
Condition: PANIC DISORDER; AGORAPHOBIA (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F40.00-F40.02,F41.0
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470, G0508-G0511,G0513,G0514,H0004,H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023, H2027,H2032,S5151,S9125,S9480,S9484,T1005

Line: 392
Condition: CROUP SYNDROME, EPIGLOTTITIS, ACUTE LARYNGOTRACHEITIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY, INTUBATION, TRACHEOTOMY
ICD-10: J04.10-J04.2,J04.31,J05.0,J05.10-J05.11
CPT: 31600,31601,31820-31830,93792,93793,94640,94664,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 393
Condition: STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN (See Coding Specification Below) (See Guideline Notes 64,65,134)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: E70.310-E70.329,H02.521-H02.529,H04.531-H04.539,H49.13,H50.00,H50.011-H50.89,H51.0,H51.11-H51.8, H53.2,H53.30-H53.34,H55.00-H55.01,H55.03,H55.09,Q10.0-Q10.7,Q11.0-Q11.3,Q13.0,Q13.2,Q13.4-Q13.5, Q13.89-Q13.9,Q14.0-Q14.9,Q15.8
CPT: 65778-65782,66820-66986,67311-67345,67901-67909,68135,68320-68328,68335,68340,68371,68810-68840, 92002-92014,92018-92065,92081-92136,92225,92226,92230-92310,92314,92325-92342,92370,93792,93793, 98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Chemodenervation with botulinum toxin injection (CPT 67345) is included on this line for the treatment of strabismus due to other neurological disorders (ICD-10 H50.89). CPT 92065 is included on Line 393 only for pairing with ICD-10 H50.31 intermittent monocular esotropia), H50.32 (Intermittent alternating esotropia), H50.33 (Intermittent monocular exotropia), and H50.34 (Intermittent alternating exotropia).

Line: 394
Condition: ANAL FISTULA (See Guideline Notes 64,65)
Treatment: SPHINCTEROTOMY, FISSURECTOMY, FISTULECTOMY, MEDICAL THERAPY
ICD-10: K60.3-K60.5
CPT: 45905,45910,46020,46030,46080,46200,46270-46288,46700,46706,46707,46940,46942,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449, 99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 395
Condition: ENDOMETRIOSIS AND ADENOMYOSIS (See Guideline Notes 39,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: N80.0-N80.9
CPT: 49203-49205,49322,58145-58150,58260-58263,58290-58292,58550-58554,58570-58573,58660-58662,58740, 58940,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285, 99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, S9560

Line: 396
Condition: ACUTE MYELOID LEUKEMIA (See Guideline Notes 7,11,12,16)
Treatment: BONE MARROW TRANSPLANT AND MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY, RADIATION AND RADIONUCLEIDE THERAPY
ICD-10: C92.00-C92.02,C92.50-C92.A2,C93.00-C93.02,C94.00-C94.6,D61.810,G89.3,Z45.49,Z48.290,Z51.0,Z51.12, Z52.000-Z52.098,Z52.3
CPT: 32553,36680,38100,38120,38204-38215,38230-38243,38760,49411,77014,77261-77290,77295,77300,77306, 77307,77321-77370,77385-77387,77401-77427,77469,77520-77525,81246,86828-86835,93792,93793,95990, 96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070, 99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498, 99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G6001-G6017,S2142,S2150,S9537

Line: **397**
Condition: MYELOID DISORDERS (See Guideline Notes 7,11,12,16)
Treatment: MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C92.00-C92.02,C92.50-C92.92,C93.00-C93.02,C93.90-C93.92,C94.00-C94.6,C95.00-C95.02,D45,D61.810, G89.3,Z45.49,Z51.0,Z51.12
CPT: 32553,38100,38120,38760,49411,77014,77261-77290,77295,77300,77306,77307,77321-77370,77385-77387, 77401-77427,77469,77520-77525,81246,93792,93793,95990,96150-96155,96377,96405,96406,96420-96450, 96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99195,99201-99239,99281-99285, 99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G6001-G6017,S9537

Line: **398**
Condition: INFLUENZA (See Guideline Notes 64,65,87)
Treatment: MEDICAL THERAPY
ICD-10: J09.X1-J09.X9,J10.00-J10.89,J11.00-J11.89
CPT: 93792,93793,94640,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404, 99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **399**
Condition: CHRONIC MYELOID LEUKEMIA
Treatment: BONE MARROW TRANSPLANT
ICD-10: C92.10-C92.22,C93.10-C93.12,C93.90-C93.92,D61.810,T86.5,Z48.290,Z52.000-Z52.098,Z52.3
CPT: 36680,38204-38215,38230-38243,86825-86835,90284,93792,93793,96377,96405,96406,96420-96440,96450, 96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, S2142,S2150,S9537

Line: **400**
Condition: BENIGN CONDITIONS OF BONE AND JOINTS AT HIGH RISK FOR COMPLICATIONS (See Guideline Notes 6,7,11,64,65,94,100,137)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: D16.00-D16.9,D17.79,D18.09,D48.1,K09.0-K09.1,M12.20,M12.211-M12.29,M27.1,M27.40-M27.49,M67.80, M67.811-M67.89,M85.40,M85.411-M85.69,Q67.6,Q79.8,Z51.0,Z51.12
CPT: 11400-11446,12051,12052,13131,17106-17111,20150,20550,20551,20600-20611,20615,20930-20938,20955-20973,21011-21014,21025-21032,21040,21046-21049,21181,21552-21556,21600,21740-21743,21930-21936, 22532-22819,22853,22854,22859,23071-23076,23101-23106,23140-23156,23200,24071-24079,24102-24126, 24420,24498,25000,25071,25073,25105,25110-25136,25170-25240,25295-25301,25320,25335,25337,25390-25393,25441-25447,25450-25492,25810-25830,26100-26116,26130,26200-26215,26250-26262,26449,27025, 27043-27049,27054,27059,27065-27078,27187,27327,27328,27334-27339,27355-27358,27365,27465-27468, 27495,27625-27638,27645-27647,27656,27745,28039-28045,28070,28072,28100-28108,28122,28124,28171-28175,28820,28825,29820,29821,29835,29836,29844,29845,29863,29875,29876,29895,29905,32553,36680, 49411,63081-63103,64774,64792,77014,77261-77295,77300-77307,77331-77338,77385-77387,77401-77427, 77469,77470,79005-79445,93792,93793,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571, 97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078, 99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513,G0514,G6001-G6017

Line: **401**
Condition: CONDITIONS OF THE BACK AND SPINE (See Guideline Notes 56,60,64,65,92,160)
Treatment: RISK ASSESSMENT, PHYSICAL MODALITIES, COGNITIVE BEHAVIORAL THERAPY, MEDICAL THERAPY
ICD-10: F45.42,G83.4,G95.0,M24.08,M25.78,M40.00-M40.15,M40.202-M40.57,M42.00-M42.09,M42.11-M42.9,M43.00-M43.4,M43.5X2-M43.5X9,M43.8X1-M43.9,M45.0-M45.9,M46.1,M46.40-M46.99,M47.011-M47.9,M48.00-M48.05, M48.061-M48.38,M48.8X1-M48.9,M49.80-M49.89,M50.00-M50.01,M50.020-M50.93,M51.04-M51.9,M53.2X1-M53.9,M54.00-M54.9,M62.830,M96.1-M96.4,M99.00-M99.09,M99.20-M99.79,M99.81-M99.84,Q06.0-Q06.3, Q06.8-Q06.9,Q68.0,Q76.0-Q76.2,Q76.411-Q76.49,S13.0XXA-S13.0XXD,S13.4XXA-S13.4XXD,S13.8XXA-S13.8XXD,S13.9XXA-S13.9XXD,S16.1XXA-S16.1XXD,S23.0XXA-S23.0XXD,S23.100A-S23.100D,S23.101A-S23.101D,S23.110A-S23.110D,S23.111A-S23.111D,S23.120A-S23.120D,S23.121A-S23.121D,S23.122A-S23.122D,S23.123A-S23.123D,S23.130A-S23.130D,S23.131A-S23.131D,S23.132A-S23.132D,S23.133A-S23.133D,S23.140A-S23.140D,S23.141A-S23.141D,S23.142A-S23.142D,S23.143A-S23.143D,S23.150A-S23.150D,S23.151A-S23.151D,S23.152A-S23.152D,S23.153A-S23.153D,S23.160A-S23.160D,S23.161A-S23.161D,S23.162A-S23.162D,S23.163A-S23.163D,S23.170A-S23.170D,S23.171A-S23.171D,S23.3XXA-S23.3XXD,S23.8XXA-S23.8XXD,S23.9XXA-S23.9XXD,S33.0XXA-S33.0XXD,S33.100A-S33.100D,S33.101A-S33.101D,S33.110A-S33.110D,S33.111A-S33.111D,S33.120A-S33.120D,S33.121A-S33.121D,S33.130A-S33.130D,S33.131A-S33.131D,S33.140A-S33.140D,S33.141A-S33.141D,S33.5XXA-S33.5XXD,S33.8XXA-

S33.8XXD,S33.9XXA-S33.9XXD,S34.3XXA-S34.3XXD,S39.092A-S39.092D,S39.82XA-S39.82XD,S39.92XA-S39.92XD
CPT: 90785,90832-90840,90853,93792,93793,96150-96155,97110-97124,97140-97168,97530,97535,97810-98942,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99304-99337,99340-99404,99408-99449,99487-99490,99495,99496,99605-99607
HCPCS: G0157-G0160,G0248-G0250,G0396,G0397,G0425-G0427,G0463-G0467,G0469,G0470,G0490,G0511,G0513,G0514,S9451

Line: **402**
Condition: LYMPHADENITIS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: I88.0-I88.8,L04.0-L04.9
CPT: 10030,10060,10061,38300-38308,38542,49405-49407,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **403**
Condition: UTERINE LEIOMYOMA AND POLYPS (See Guideline Notes 40,64,65)
Treatment: SURGICAL TREATMENT
ICD-10: D25.0-D25.9,D26.0-D26.9,D39.0,N84.0,N84.8-N84.9,N85.2-N85.3
CPT: 37243,58120-58180,58260-58263,58290-58292,58541-58554,58559,58561,58570-58573,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9560

Line: **404**
Condition: APHAKIA AND OTHER DISORDERS OF LENS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL THERAPY
ICD-10: H27.00-H27.10,H27.111-H27.8
CPT: 65750,65765,65767,66825,66985-66990,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,92311,92312,92352,92353,92358,92371,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **405**
Condition: BILATERAL ANOMALIES OF EXTERNAL EAR WITH IMPAIRMENT OF HEARING (See Guideline Notes 64,65)
Treatment: RECONSTRUCT OF EAR CANAL
ICD-10: H61.301-H61.399,Q16.0-Q16.1,Q16.3-Q16.9,Z01.12
CPT: 69310,69320,69631-69637,92562-92565,92571-92577,92590,92591,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **406**
Condition: DISSOCIATIVE DISORDERS (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F44.0-F44.2,F44.81-F44.89,F48.1
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005

Line: **407**
Condition: EPIDERMOLYSIS BULLOSA (See Guideline Notes 6,64,65)
Treatment: MEDICAL THERAPY
ICD-10: Q81.0-Q81.9
CPT: 11000,11001,93792,93793,96150-96155,96900,96902,96910-96913,97012,97110-97124,97140-97168,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **408**
Condition: DELIRIUM DUE TO MEDICAL CAUSES (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: F05
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **409**
Condition: MIGRAINE HEADACHES (See Guideline Notes 42,64,65,92)
Treatment: MEDICAL THERAPY
ICD-10: G43.001-G43.719,G43.B0-G43.C1,G43.801-G43.919,G44.001-G44.1
CPT: 64615,92002-92014,92081-92083,93792,93793,96150-96155,97810-97814,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **410**
Condition: DENTAL CONDITIONS (E.G., PULPAL PATHOLOGY, PERMANENT BICUSPID/PREMOLAR TOOTH)
Treatment: BASIC ENDODONTICS (I.E., ROOT CANAL THERAPY)
HCPCS: D3320,D3332

Line: **411**
Condition: SCHIZOTYPAL PERSONALITY DISORDERS (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F21
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0018,H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005

Line: **412**
Condition: BALANOPOSTHITIS AND OTHER DISORDERS OF PENIS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: N47.2,N47.6,N48.1,N48.5
CPT: 53431,54000-54015,54110-54112,54200,54205,54230,54231,54240,54250,54450,74445,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **413**
Condition: OVERANXIOUS DISORDER; GENERALIZED ANXIETY DISORDER; ANXIETY DISORDER, UNSPECIFIED (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F41.1-F41.9
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0019,H0023,H0032-H0034,H0036-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,H2033,S5151,S9125,S9484,T1005

Line: **414**
Condition: TRANSIENT CEREBRAL ISCHEMIA; OCCLUSION/STENOSIS OF PRECEREBRAL ARTERIES WITHOUT OCCLUSION (See Guideline Notes 64,65,119,125)
Treatment: MEDICAL THERAPY; THROMBOENDARTERECTOMY
ICD-10: G45.0-G45.3,G45.8-G45.9,G46.0-G46.2,H34.00-H34.03,H93.011-H93.019,I65.01-I65.9,I66.01-I66.9,I77.71,I77.74-I77.75,Z86.73
CPT: 34001,35301,35390,35606,37215-37218,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 415
Condition: PERIPHERAL NERVE ENTRAPMENT; PALMAR FASCIAL FIBROMATOSIS (See Guideline Notes 6,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: G56.00-G56.03,G56.20-G56.23,G57.30-G57.53,M53.1,M72.0
CPT: 20526,25109,25111,25118,25447,26035,26045,26060,26121-26180,26320,26440-26498,28035,29105,29515, 29848,64702,64704,64718-64727,64774-64783,64788-64792,64856,64857,64872-64907,93792,93793,97012, 97018,97110-97124,97140-97168,97530,98925-98942,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513,G0514

Line: 416
Condition: MENIERE'S DISEASE (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: H81.01-H81.09
CPT: 69666,69667,69801-69806,69915,69950,92531-92548,93792,93793,96150-96155,98966-98969,99051,99060, 99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 417
Condition: DISORDERS OF SHOULDER, INCLUDING SPRAINS/STRAINS GRADE 4 THROUGH 6 (See Guideline Notes 6,64,65,97)
Treatment: REPAIR/RECONSTRUCTION, MEDICAL THERAPY
ICD-10: M24.011-M24.019,M24.111-M24.119,M24.311-M24.319,M24.611-M24.619,M24.811-M24.819,M25.211-M25.219, M25.311-M25.319,M25.711-M25.719,M66.211-M66.219,M66.811-M66.819,M75.00-M75.02,M75.100-M75.122, M75.30-M75.92,S43.401A-S43.401D,S43.402A-S43.402D,S43.409A-S43.409D,S43.411A-S43.411D,S43.412A-S43.412D,S43.419A-S43.419D,S43.421A-S43.421D,S43.422A-S43.422D,S43.429A-S43.429D,S43.431A-S43.431D,S43.432A-S43.432D,S43.439A-S43.439D,S43.491A-S43.491D,S43.492A-S43.492D,S43.499A-S43.499D,S43.50XA-S43.50XD,S43.51XA-S43.51XD,S43.52XA-S43.52XD,S43.60XA-S43.60XD,S43.61XA-S43.61XD,S43.62XA-S43.62XD,S43.80XA-S43.80XD,S43.81XA-S43.81XD,S43.82XA-S43.82XD,S43.90XA-S43.90XD,S43.91XA-S43.91XD,S43.92XA-S43.92XD,S46.011A-S46.011D,S46.012A-S46.012D,S46.019A-S46.019D,S46.111A-S46.111D,S46.112A-S46.112D,S46.119A-S46.119D,S46.211A-S46.211D,S46.212A-S46.212D,S46.219A-S46.219D,S46.311A-S46.311D,S46.312A-S46.312D,S46.319A-S46.319D,S46.811A-S46.811D,S46.812A-S46.812D,S46.819A-S46.819D,S46.911A-S46.911D,S46.912A-S46.912D,S46.919A-S46.919D,Z47.31
CPT: 20550,20610,20611,20615,23000,23020,23105-23130,23190,23195,23334,23335,23395,23410-23460,23490, 23491,23650-23700,29807-29828,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98925-98942,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404, 99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513,G0514

Line: 418
Condition: CHRONIC LEUKEMIAS WITH POOR PROGNOSIS (See Guideline Notes 7,11,12)
Treatment: MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY, RADIATION AND RADIONUCLEIDE THERAPY
ICD-10: C91.10-C91.92,C93.Z0-C93.Z2,C94.80-C94.82,C95.10-C95.92,D61.810,G89.3,Z51.0,Z51.12
CPT: 32553,49411,77014,77261-77290,77295,77300,77306,77307,77321-77370,77385-77387,77401-77417,77424-77427,77469,79101,90284,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570, 96571,98966-98969,99051,99060,99070,99078,99184,99195,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G6001-G6017,S9537

Line: 419
Condition: OPPOSITIONAL DEFIANT DISORDER (See Guideline Notes 64,65,152)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F91.3,F91.9
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224, 99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513, G0514,H0004,H0017-H0019,H0023,H0032-H0034,H0036-H0039,H0045,H2010,H2012,H2014,H2021,H2022, H2027,H2032,H2033,S5151,S9125,S9480,S9484,T1005

Line: **420**
Condition: MENSTRUAL BLEEDING DISORDERS (See Guideline Notes 44,64,65,88)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: N85.01,N85.5,N92.0-N92.6,Q51.5
CPT: 57800,58120,58150,58180,58260,58262,58290,58291,58300,58301,58353,58356,58541-58544,58550-58554, 58561-58563,58570-58573,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **421**
Condition: LYMPHEDEMA (See Guideline Notes 6,43,64,65,149)
Treatment: MEDICAL THERAPY, OTHER OPERATION ON LYMPH CHANNEL
ICD-10: I89.0,I89.8-I89.9,I97.2,Q82.0
CPT: 29581,29584,38300-38382,38542-38555,38700-38745,38747,38760,49062,49185,49323,49423,93792,93793, 97016,97110,97124,97140,97161-97168,97530,97760,97763,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **422**
Condition: COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT (See Coding Specification Below) (See Guideline Notes 6,62,64,65,149,157)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: D78.31-D78.89,E36.8,E89.810-E89.89,G89.22,G96.11,G97.1,G97.41,H59.011-H59.099,H59.811-H59.89, H74.8X1-H74.8X9,H95.811-H95.89,I97.3,J95.00,K91.61-K91.62,K91.840-K91.858,K94.00,K94.03-K94.10,K94.13-K94.20,K94.23-K94.30,K94.32-K94.39,K95.09-K95.89,L27.0,L58.0,L64.0,L65.8,L76.01-L76.02,L76.21-L76.82, M96.810-M96.811,M96.830-M96.89,N98.1-N98.9,N99.110-N99.114,N99.61-N99.62,N99.820-N99.821,N99.840-N99.843,O89.4,T66.XXXA-T66.XXXD,T80.1XXA-T80.1XXD,T80.30XA-T80.30XD,T80.310A-T80.310D,T80.311A-T80.311D,T80.319A-T80.319D,T80.39XA-T80.39XD,T80.40XA-T80.40XD,T80.410A-T80.410D,T80.411A-T80.411D,T80.419A-T80.419D,T80.49XA-T80.49XD,T80.A0XA-T80.A0XD,T80.A10A-T80.A10D,T80.A11A-T80.A11D,T80.A19A-T80.A19D,T80.A9XA-T80.A9XD,T80.61XA-T80.61XD,T80.62XA-T80.62XD,T80.69XA-T80.69XD,T81.500A-T81.500D,T81.501A-T81.501D,T81.502A-T81.502D,T81.503A-T81.503D,T81.504A-T81.504D,T81.505A-T81.505D,T81.506A-T81.506D,T81.507A-T81.507D,T81.508A-T81.508D,T81.509A-T81.509D,T81.510A-T81.510D,T81.511A-T81.511D,T81.512A-T81.512D,T81.513A-T81.513D,T81.514A-T81.514D,T81.515A-T81.515D,T81.516A-T81.516D,T81.517A-T81.517D,T81.518A-T81.518D,T81.519A-T81.519D,T81.527A-T81.527D,T81.528A-T81.528D,T81.529A-T81.529D,T81.530A-T81.530D,T81.531A-T81.531D,T81.532A-T81.532D,T81.533A-T81.533D,T81.534A-T81.534D,T81.535A-T81.535D,T81.536A-T81.536D,T81.537A-T81.537D,T81.538A-T81.538D,T81.539A-T81.539D,T81.590A-T81.590D,T81.591A-T81.591D,T81.592A-T81.592D,T81.593A-T81.593D,T81.594A-T81.594D,T81.595A-T81.595D,T81.596A-T81.596D,T81.597A-T81.597D,T81.598A-T81.598D,T81.599A-T81.599D,T81.60XA-T81.60XD,T81.61XA-T81.61XD,T81.69XA-T81.69XD,T81.89XA-T81.89XD,T83.018A-T83.018D,T83.021A-T83.021D,T83.028A-T83.028D,T83.031A-T83.031D,T83.038A-T83.038D,T83.091A-T83.091D,T83.098A-T83.098D,T83.31XA-T83.31XD,T83.32XA-T83.32XD,T83.39XA-T83.39XD,T83.411A-T83.411D,T83.421A-T83.421D,T83.491A-T83.491D,T83.711A-T83.711D,T83.712A-T83.712D,T83.713A-T83.713D,T83.714A-T83.714D,T83.718A-T83.718D,T83.719A-T83.719D,T83.721A-T83.721D,T83.722A-T83.722D,T83.723A-T83.723D,T83.724A-T83.724D,T83.728A-T83.728D,T83.729A-T83.729D,T83.79XA-T83.79XD,T85.21XA-T85.21XD,T85.22XA-T85.22XD,T85.29XA-T85.29XD,T85.310A-T85.310D,T85.311A-T85.311D,T85.318A-T85.318D,T85.320A-T85.320D,T85.321A-T85.321D,T85.328A-T85.328D,T85.390A-T85.390D,T85.391A-T85.391D,T85.398A-T85.398D,T85.41XA-T85.41XD,T85.42XA-T85.42XD,T85.43XA-T85.43XD,T85.44XA-T85.44XD,T85.49XA-T85.49XD,T85.510A-T85.510D,T85.511A-T85.511D,T85.518A-T85.518D,T85.520A-T85.520D,T85.521A-T85.521D,T85.528A-T85.528D,T85.590A-T85.590D,T85.591A-T85.591D,T85.598A-T85.598D,T85.610A-T85.610D,T85.612A-T85.612D,T85.613A-T85.613D,T85.614A-T85.614D,T85.618A-T85.618D,T85.620A-T85.620D,T85.622A-T85.622D,T85.623A-T85.623D,T85.624A-T85.624D,T85.628A-T85.628D,T85.630A-T85.630D,T85.633A-T85.633D,T85.638A-T85.638D,T85.690A-T85.690D,T85.692A-T85.692D,T85.693A-T85.693D,T85.694A-T85.694D,T85.698A-T85.698D,T85.840A-T85.840D,T85.848A-T85.848D,T86.820-T86.829, T87.30-T87.34,T87.81-T87.9,T88.52XA-T88.52XD,T88.53XA-T88.53XD,T88.59XA-T88.59XD,T88.8XXA-T88.8XXD,Z45.42,Z45.82,Z47.32-Z47.33
CPT: 10030,10140,10160,11042-11047,11976,11982,11983,13160,15002-15005,19328,19330,19371,19380,20661, 20680,20694,21120,21501,22849-22852,22855,24160,24164,25250,25251,25449,25909,26320,26990,27090, 27091,27132-27138,27265,27266,27301,27486-27488,27570,27603,27704,27884,27886,29584,31613,31614, 31630,31631,31636-31638,31641,31645,31750-31781,31800-31830,33922,35875,35876,35901-35905,36860, 36861,37224,37228,43285,43771-43774,43848,43870,44227,44312,44314,44340-44346,44620-44626,47536, 47537,49185,49422,49429,53442,53446-53449,57295,57296,58301,58562,62100,62273,63661-63664,63688, 63707,63709,64595,64788,65150-65175,65920,66825,66985,66986,67036,67121,67560,69424,69711,75984, 92002-92014,92507,92508,92521-92526,92607-92609,92633,93792,93793,97012,97110-97124,97140-97168, 97530,97535,97542,97605-97608,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239, 99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: A9282,G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9152

ICD-10-CM codes L58.0, L64.0 and L65.8 are only included on this line for pairing with HCPC A9282.

Line: **423**
Condition: ADRENOGENITAL DISORDERS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: E25.0-E25.9,Q56.0-Q56.4
CPT: 50700,54690,56800-56810,57335,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239, 99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **424**
Condition: SEVERE INFLAMMATORY SKIN DISEASE (See Coding Specification Below) (See Guideline Note 21)
Treatment: MEDICAL THERAPY
ICD-10: H01.121-H01.129,L20.82-L20.9,L40.0-L40.4,L40.8-L40.9,L41.0-L41.9,L43.0-L43.9,L44.0,L93.0,Q82.8
CPT: 93792,93793,96150-96155,96900,96902,96910-96922,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

ICD-10-CM Q82.8 is included on this line only for Darier disease.

Line: **425**
Condition: ACUTE PERIPHERAL MOTOR AND DIGITAL NERVE INJURY (See Guideline Note 133)
Treatment: SURGICAL THERAPY
ICD-10: G57.20-G57.23,S74.00XA-S74.00XD,S74.01XA-S74.01XD,S74.02XA-S74.02XD,S74.10XA-S74.10XD,S74.11XA-S74.11XD,S74.12XA-S74.12XD
CPT: 20550,20551,21032,24105,24357-24359,25109,25447,26035,26060,26121-26180,26320,26440-26556,26565-26596,26820-26863,27060,27097,27100-27122,27140-27165,27306,27307,27448-27455,27466,27468,27475-27485,27715,27730-27742,28119,64702,64704,64718-64727,64774,64856,64857,64872-64907,93792,93793, 98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513,G0514

Line: **426**
Condition: NON-MALIGNANT OTITIS EXTERNA (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: B37.84,H60.311-H60.399,H62.40-H62.43
CPT: 69000,69020,69209,69210,92633,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **427**
Condition: VAGINITIS AND CERVICITIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: A56.02,A59.00-A59.9,B37.3,N72,N76.0-N76.3,N77.1,N89.8
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **428**
Condition: NONINFLAMMATORY DISORDERS AND BENIGN NEOPLASMS OF OVARY, FALLOPIAN TUBES AND UTERUS; OVARIAN CYSTS; GONADAL DYSGENISIS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: D27.0-D27.9,D28.2,N83.00-N83.12,N83.201-N83.299,N83.40-N83.42,N83.7,Q50.01-Q50.39
CPT: 49322,58559,58561,58562,58660-58662,58700-58740,58800,58805,58900-58943,93792,93793,98966-98969, 99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **429**
Condition: URETHRAL FISTULA (See Guideline Notes 64,65)
Treatment: EXCISION, MEDICAL THERAPY
ICD-10: N36.0-N36.1,N36.5
CPT: 45820,53230-53250,53520,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **430**
Condition: INTERNAL DERANGEMENT OF KNEE AND LIGAMENTOUS DISRUPTIONS OF THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT (See Guideline Notes 6,64,65,98,104)
Treatment: REPAIR, MEDICAL THERAPY
ICD-10: M22.2X1-M22.3X9,M22.8X1-M22.8X9,M23.011-M23.205,M23.211-M23.305,M23.311-M23.8X9,M24.661-M24.669,M66.261-M66.269,S83.200A-S83.200D,S83.201A-S83.201D,S83.202A-S83.202D,S83.203A-S83.203D,S83.204A-S83.204D,S83.205A-S83.205D,S83.206A-S83.206D,S83.207A-S83.207D,S83.209A-S83.209D,S83.211A-S83.211D,S83.212A-S83.212D,S83.219A-S83.219D,S83.221A-S83.221D,S83.222A-S83.222D,S83.229A-S83.229D,S83.231A-S83.231D,S83.232A-S83.232D,S83.239A-S83.239D,S83.241A-S83.241D,S83.242A-S83.242D,S83.249A-S83.249D,S83.251A-S83.251D,S83.252A-S83.252D,S83.259A-S83.259D,S83.261A-S83.261D,S83.262A-S83.262D,S83.269A-S83.269D,S83.271A-S83.271D,S83.272A-S83.272D,S83.279A-S83.279D,S83.281A-S83.281D,S83.282A-S83.282D,S83.289A-S83.289D,S83.30XA-S83.30XD,S83.31XA-S83.31XD,S83.32XA-S83.32XD,S83.401A-S83.401D,S83.402A-S83.402D,S83.409A-S83.409D,S83.411A-S83.411D,S83.412A-S83.412D,S83.419A-S83.419D,S83.421A-S83.421D,S83.422A-S83.422D,S83.429A-S83.429D,S83.501A-S83.501D,S83.502A-S83.502D,S83.509A-S83.509D,S83.511A-S83.511D,S83.512A-S83.512D,S83.519A-S83.519D,S83.521A-S83.521D,S83.522A-S83.522D,S83.529A-S83.529D,S83.60XA-S83.60XD,S83.61XA-S83.61XD,S83.62XA-S83.62XD,S83.8X1A-S83.8X1D,S83.8X2A-S83.8X2D,S83.8X9A-S83.8X9D,S83.90XA-S83.90XD,S83.91XA-S83.91XD,S83.92XA-S83.92XD,S86.111A-S86.111D,S86.112A-S86.112D,S86.119A-S86.119D,S86.211A-S86.211D,S86.212A-S86.212D,S86.219A-S86.219D,S86.311A-S86.311D,S86.312A-S86.312D,S86.319A-S86.319D,S86.811A-S86.811D,S86.812A-S86.812D,S86.819A-S86.819D,S86.911A-S86.911D,S86.912A-S86.912D,S86.919A-S86.919D
CPT: 20610,20611,27332-27335,27340,27350,27380,27381,27403-27416,27420-27430,27570,29345-29445,29505,29530,29705,29871-29889,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **431**
Condition: PERSISTENT DEPRESSIVE DISORDER (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F34.1
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0023,H0032-H0034,H0036-H0039,H0045,H2010,H2012,H2014,H2021-H2023,H2027,H2032,H2033,S9480,S9484

Line: **432**
Condition: HYPOSPADIAS AND EPISPADIAS (See Guideline Notes 64,65,72,73)
Treatment: REPAIR
ICD-10: Q54.0-Q54.8,Q55.5,Q55.61-Q55.69,Q64.0,S39.840A-S39.840D
CPT: 51715,53431,54230,54231,54240-54390,54420,54430,54440,55175,55180,74445,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **433**
Condition: CANCER OF GALLBLADDER AND OTHER BILIARY (See Guideline Notes 7,11,12,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: C23,C24.0-C24.9,D01.5,D61.810,G89.3,Z51.0,Z51.11-Z51.12
CPT: 32553,43260-43265,43273-43278,47533-47540,47542,47562-47570,47600-47620,47711,47712,47741,47785,48145-48155,49327,49411,49412,60540,77014,77261-77290,77295,77300,77306-77370,77385-77387,77402-77417,77424-77432,77469,77470,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

Line: **434**
Condition: PRECANCEROUS VULVAR CONDITIONS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: L90.0,N90.0-N90.1,N90.4-N90.5
CPT: 56501,56515,56620,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **435**
Condition: RECURRENT EROSION OF THE CORNEA (See Guideline Notes 64,65)
Treatment: ANTERIAL STROMAL PUNCTURE, REMOVAL OF CORNEAL EPITHELIUM; WITH OR WITHOUT CHEMOCAUTERIZATION
ICD-10: H18.831-H18.839
CPT: 65430,65435,65600,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **436**
Condition: STEREOTYPED MOVEMENT DISORDER WITH SELF-INJURIOUS BEHAVIOR DUE TO NEURODEVELOPMENTAL DISORDER (See Guideline Notes 64,65,126)
Treatment: CONSULTATION/MEDICATION MANAGEMENT/LIMITED BEHAVIORAL MODIFICATION
ICD-10: F98.4
CPT: 0359T-0374T,90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99281-99285,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017,H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005

Line: **437**
Condition: FOREIGN BODY IN UTERUS, VULVA AND VAGINA (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: T19.2XXA-T19.2XXD,T19.3XXA-T19.3XXD
CPT: 57415,58120,58562,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **438**
Condition: RESIDUAL FOREIGN BODY IN SOFT TISSUE
Treatment: REMOVAL
ICD-10: H02.811-H02.819,M79.5,Z18.01-Z18.89
CPT: 10120,10121,20520,20525,23330,23333,24200,24201,25248,27086,27087,27372,28190-28193,40804,41805,55120,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **439**
Condition: VENOUS TRIBUTARY (BRANCH) OCCLUSION; CENTRAL RETINAL VEIN OCCLUSION (See Guideline Notes 64,65,116)
Treatment: SURGICAL TREATMENT INCLUDING LASER SURGERY, MEDICAL THERAPY INCLUDING INJECTION
ICD-10: H34.8110-H34.8192,H34.8310-H34.9
CPT: 67028,67228,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **440**
Condition: TRIGEMINAL AND OTHER NERVE DISORDERS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES RADIATION THERAPY
ICD-10: G50.0-G50.9,G52.0-G52.9,G53,Z45.42,Z51.0
CPT: 32553,49411,61450,61458,61790-61800,64568-64570,64600-64610,64716,77014,77261-77295,77300,77301,77332-77372,77402,77417-77432,77469,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **441**
Condition: MALUNION AND NONUNION OF FRACTURE (See Guideline Notes 6,64,65)
Treatment: SURGICAL TREATMENT
ICD-10: M80.00XK-M80.00XP,M80.011K-M80.011P,M80.012K-M80.012P,M80.019K-M80.019P,M80.021K-M80.021P,M80.022K-M80.022P,M80.029K-M80.029P,M80.031K-M80.031P,M80.032K-M80.032P,M80.039K-M80.039P,M80.041K-M80.041P,M80.042K-M80.042P,M80.049K-M80.049P,M80.051K-M80.051P,M80.052K-M80.052P,M80.059K-M80.059P,M80.061K-M80.061P,M80.062K-M80.062P,M80.069K-M80.069P,M80.071K-M80.071P,M80.072K-M80.072P,M80.079K-M80.079P,M80.08XK-M80.08XP,M80.80XK-M80.80XP,M80.811K-M80.811P,M80.812K-M80.812P,M80.819K-M80.819P,M80.821K-M80.821P,M80.822K-M80.822P,M80.829K-M80.829P,M80.831K-M80.831P,M80.832K-M80.832P,M80.839K-M80.839P,M80.841K-M80.841P,M80.842K-M80.842P,

M80.849K-M80.849P,M80.851K-M80.851P,M80.852K-M80.852P,M80.859K-M80.859P,M80.861K-M80.861P,
M80.862K-M80.862P,M80.869K-M80.869P,M80.871K-M80.871P,M80.872K-M80.872P,M80.879K-M80.879P,
M80.88XK-M80.88XP,M84.30XK-M84.30XP,M84.311K-M84.311P,M84.312K-M84.312P,M84.319K-M84.319P,
M84.321K-M84.321P,M84.322K-M84.322P,M84.329K-M84.329P,M84.331K-M84.331P,M84.332K-M84.332P,
M84.333K-M84.333P,M84.334K-M84.334P,M84.339K-M84.339P,M84.341K-M84.341P,M84.342K-M84.342P,
M84.343K-M84.343P,M84.344K-M84.344P,M84.345K-M84.345P,M84.346K-M84.346P,M84.350K-M84.350P,
M84.351K-M84.351P,M84.352K-M84.352P,M84.353K-M84.353P,M84.359K-M84.359P,M84.361K-M84.361P,
M84.362K-M84.362P,M84.363K-M84.363P,M84.364K-M84.364P,M84.369K-M84.369P,M84.371K-M84.371P,
M84.372K-M84.372P,M84.373K-M84.373P,M84.374K-M84.374P,M84.375K-M84.375P,M84.376K-M84.376P,
M84.377K-M84.377P,M84.378K-M84.378P,M84.379K-M84.379P,M84.38XK-M84.38XP,M84.40XK-M84.40XP,
M84.411K-M84.411P,M84.412K-M84.412P,M84.419K-M84.419P,M84.421K-M84.421P,M84.422K-M84.422P,
M84.429K-M84.429P,M84.431K-M84.431P,M84.432K-M84.432P,M84.433K-M84.433P,M84.434K-M84.434P,
M84.439K-M84.439P,M84.441K-M84.441P,M84.442K-M84.442P,M84.443K-M84.443P,M84.444K-M84.444P,
M84.445K-M84.445P,M84.446K-M84.446P,M84.451K-M84.451P,M84.452K-M84.452P,M84.453K-M84.453P,
M84.454K-M84.454P,M84.459K-M84.459P,M84.461K-M84.461P,M84.462K-M84.462P,M84.463K-M84.463P,
M84.464K-M84.464P,M84.469K-M84.469P,M84.471K-M84.471P,M84.472K-M84.472P,M84.473K-M84.473P,
M84.474K-M84.474P,M84.475K-M84.475P,M84.476K-M84.476P,M84.477K-M84.477P,M84.478K-M84.478P,
M84.479K-M84.479P,M84.48XK-M84.48XP,M84.50XK-M84.50XP,M84.511K-M84.511P,M84.512K-M84.512P,
M84.519K-M84.519P,M84.521K-M84.521P,M84.522K-M84.522P,M84.529K-M84.529P,M84.531K-M84.531P,
M84.532K-M84.532P,M84.533K-M84.533P,M84.534K-M84.534P,M84.539K-M84.539P,M84.541K-M84.541P,
M84.542K-M84.542P,M84.549K-M84.549P,M84.550K-M84.550P,M84.551K-M84.551P,M84.552K-M84.552P,
M84.553K-M84.553P,M84.559K-M84.559P,M84.561K-M84.561P,M84.562K-M84.562P,M84.563K-M84.563P,
M84.564K-M84.564P,M84.569K-M84.569P,M84.571K-M84.571P,M84.572K-M84.572P,M84.573K-M84.573P,
M84.574K-M84.574P,M84.575K-M84.575P,M84.576K-M84.576P,M84.58XK-M84.58XP,M84.60XK-M84.60XP,
M84.611K-M84.611P,M84.612K-M84.612P,M84.619K-M84.619P,M84.621K-M84.621P,M84.622K-M84.622P,
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CPT: 20680-20694,20955-20975,21244,21462,21750,21825,23472-23485,24130,24140,24400,24410,24430,24435, 25259,25400-25440,25628,26185,26546,26565,26567,26735,26841,27125-27132,27165,27170,27217,27236, 27465-27472,27656,27707,27720-27726,27824-27829,27880-27888,28315-28322,28485,28725,29075,29085, 29130,29345,29405,29425,29825,29826,29904-29907,93792,93793,97012,97110-97124,97140-97168,97530, 97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513,G0514

Line: **442**
Condition: DENTAL CONDITIONS (E.G., PULPAL PATHOLOGY, PERMANENT MOLAR TOOTH)
Treatment: BASIC ENDODONTICS (I.E., ROOT CANAL THERAPY)
HCPCS: D3330,D3332

Line: **443**
Condition: ADJUSTMENT DISORDERS (See Coding Specification Below) (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F43.20-F43.8,F98.9,Z62.810-Z62.898,Z63.4,Z63.8,Z71.89
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224, 99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0023,H0032-H0038,H0045,H2010,H2012,H2014,H2021-H2023,H2027,H2032,H2033,S5151,S9125,S9484,T1005

ICD-10-CM codes Z71.89, Other specified counseling, and Z63.4 Disappearance and death of family member are only included in this line when identified as secondary diagnoses with a primary diagnosis of F43.8, Other reactions to severe stress.

Line: **444**
Condition: HEARING LOSS - OVER AGE OF FIVE (See Guideline Notes 51,64,65,103,143,154)
Treatment: MEDICAL THERAPY INCLUDING HEARING AIDS, LIMITED SURGICAL THERAPY
ICD-10: H72.00-H72.13,H72.2X1-H72.93,H83.3X1-H83.3X9,H90.0,H90.11-H90.8,H90.A11-H90.A32,H91.01-H91.3, H91.8X1-H91.93,H93.091-H93.099,H93.211-H93.249,H93.291-H93.3X9,H94.00-H94.03,S09.20XA-S09.20XD, S09.21XA-S09.21XD,S09.22XA-S09.22XD,Z01.12,Z46.1
CPT: 42830,42835,69209,69210,69433,69436,69610-69646,69714-69718,92562-92565,92571-92577,92590-92595, 92597,92626,92627,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **445**
Condition: TOURETTE'S DISORDER AND TIC DISORDERS (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F95.0-F95.9
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,96150-96155,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513, G0514,H0004,H0023,H0032-H0034,H0036-H0038,H2010,H2012-H2014,H2021,H2022,H2027,H2032,S9484

Line: **446**
Condition: ATHEROSCLEROSIS, AORTIC AND RENAL (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: I70.0-I70.1
CPT: 35501-35515,35526,35531,35535-35540,35560,35563,35572,35601-35616,35626-35647,35654,35663,35697, 35820,35840,35875,35876,35905,35907,37184-37186,37211,37213,37214,37236,37237,37246,37247,93792, 93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404, 99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **447**
Condition: DEGENERATION OF MACULA AND POSTERIOR POLE (See Guideline Notes 46,64,65)
Treatment: MEDICAL, SURGICAL AND LASER TREATMENT
ICD-10: H31.101-H31.20,H31.22-H31.29,H31.301-H31.319,H35.30,H35.3110-H35.389,H35.81,H44.20-H44.23,H44.2A1-H44.2B9,H44.2D1-H44.2E9
CPT: 66990,67028,67039-67043,67210,67221,67225,67515,92002-92014,92018-92060,92081-92136,92225,92226, 92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 448
Condition: REACTIVE ATTACHMENT DISORDER OF INFANCY OR EARLY CHILDHOOD (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F94.1-F94.2
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0038,H0045,H2010,H2012-H2014,H2021,H2022,H2027,H2032,S5151,S9125,S9484,T1005

Line: 449
Condition: DISORDERS OF REFRACTION AND ACCOMMODATION (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: H52.00-H52.13,H52.201-H52.7,H53.10-H53.11,H53.16-H53.19,H53.50-H53.69,Z46.0
CPT: 92002-92060,92081-92136,92225,92226,92230-92310,92314,92325-92342,92370,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: 450
Condition: EXOPHTHALMOS AND CYSTS OF THE EYE AND ORBIT (See Guideline Notes 64,65)
Treatment: SURGICAL TREATMENT
ICD-10: H05.20,H05.211-H05.359,H05.811-H05.819,H21.311-H21.329,H21.341-H21.359
CPT: 67405-67414,67420-67440,67875-67882,68500,68505,68540,68550,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 451
Condition: DENTAL CONDITIONS (E.G., MISSING TEETH, PROSTHESIS FAILURE) (See Guideline Note 117)
Treatment: REMOVABLE PROSTHODONTICS (E.G., FULL AND PARTIAL DENTURES, RELINES)
ICD-10: K00.0,K08.101-K08.122,K08.124-K08.199,K08.401-K08.499
HCPCS: D5110-D5212,D5221,D5222,D5511-D5761,D5820,D5821,D7472,D7473,D7970

Line: 452
Condition: RECTAL PROLAPSE (See Guideline Notes 64,65)
Treatment: SURGICAL TREATMENT
ICD-10: K62.2-K62.4
CPT: 44139-44144,44204-44208,44213,44701,45130,45135,45303,45340,45400,45402,45505-45541,45900,46080,46500,46604,46700,46705,46750,46751,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 453
Condition: URINARY INCONTINENCE (See Guideline Notes 6,47,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: N36.41-N36.43,N39.3,N39.41-N39.42,N39.46,N39.490-N39.498,R39.81
CPT: 51840-51845,51990,51992,53446,53448,57160,57220,57260,57267,57280-57289,57423,57425,90911,93792,93793,96150-96155,97110,97140,97161-97164,97530,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 454
Condition: DISORDERS OF PLASMA PROTEIN METABOLISM (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: D89.0-D89.2,E88.01-E88.09
CPT: 36514,36516,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 455
Condition: DENTAL CONDITIONS (E.G., PULPAL PATHOLOGY, PERMANENT ANTERIOR TOOTH)
Treatment: ADVANCED ENDODONTICS (E.G., RETREATMENT OF PREVIOUS ROOT CANAL THERAPY)
HCPCS: D3331,D3333,D3346,D3410,D3430

Line: 456
Condition: SIMPLE PHOBIAS AND SOCIAL ANXIETY DISORDER (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F40.10-F40.11,F40.210-F40.9
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0023,H0032-H0038,H2010,H2012,H2014,H2021-H2023,H2027,H2032,H2033,S9484

Line: 457
Condition: ACUTE BRONCHITIS AND BRONCHIOLITIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: B25.0,J20.0-J20.9,J21.0-J21.9,J98.01
CPT: 31600,31601,31820,31825,93792,93793,94640,94664,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 458
Condition: CENTRAL PTERYGIUM AFFECTING VISION (See Guideline Notes 64,65)
Treatment: EXCISION OR TRANSPOSITION OF PTERYGIUM WITHOUT GRAFT, RADIATION THERAPY
ICD-10: H11.021-H11.029,Z51.0
CPT: 32553,49411,65420,65426,77316-77318,77332-77370,77402,77424-77427,77469,77789,79005-79445,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 459
Condition: BRANCHIAL CLEFT CYST; THYROGLOSSAL DUCT CYST; CYST OF PHARYNX OR NASOPHARYNX (See Guideline Notes 64,65)
Treatment: EXCISION, MEDICAL THERAPY
ICD-10: J39.2,K09.0-K09.1,Q18.0-Q18.2,Q89.2
CPT: 38550,38555,42808,42810,42815,60000,60280,60281,69145,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 460
Condition: OBSESSIVE-COMPULSIVE DISORDERS (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F42.2-F42.9,F45.22,F63.3
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0019,H0023,H0032-H0034,H0036-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S9480,S9484,T1005

Line: 461
Condition: OSTEOARTHRITIS AND ALLIED DISORDERS (See Guideline Notes 6,64,65,92,104)
Treatment: MEDICAL THERAPY, INJECTIONS
ICD-10: M12.10,M12.111-M12.19,M12.40,M12.411-M12.59,M13.80,M13.811-M13.89,M15.0-M15.9,M16.0,M16.10-M16.9,M17.0,M17.10-M17.9,M18.0,M18.10-M18.9,M19.011-M19.93,M20.20-M20.22,M24.171-M24.176,M24.671-M24.673,M24.871-M24.872,M24.874-M24.875,M25.871-M25.879
CPT: 11042,11045,20600-20611,25000,29075,93792,93793,96150-96155,97012,97018,97110-97124,97140-97168,97530,97535,97542,97760-97763,97810-98942,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 462
Condition: ATELECTASIS (COLLAPSE OF LUNG) (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: J18.2,J98.11-J98.19
CPT: 31645,31646,93792,93793,94002-94005,94640,94660-94668,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 463
Condition: CHRONIC SINUSITIS (See Guideline Notes 35,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: J01.01,J01.11,J01.21,J01.31,J01.41,J01.81,J01.91,J32.0-J32.9
CPT: 30000,30020,30110-30140,30200-30420,30435,30450,30465-30930,31000-31230,31237-31298,42830,42835,61782,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 464
Condition: UTERINE PROLAPSE; CYSTOCELE (See Guideline Notes 6,50,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: N81.0,N81.10-N81.9,N99.3
CPT: 45560,51840,52270,52285,53000,53010,56810,57106,57120,57160,57220-57289,57423,57425,57545,57555,57556,58150,58152,58260-58280,58290-58294,58550-58554,58570-58573,93792,93793,97110,97140,97161-97164,97530,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 465
Condition: BRACHIAL PLEXUS LESIONS (See Guideline Notes 6,64,65)
Treatment: MEDICAL THERAPY
ICD-10: G54.0
CPT: 21615,21616,21700,21705,93792,93793,97110,97112,97116,97124,97140,97161-97168,98925-98942,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 466
Condition: DENTAL CONDITIONS (E.G., CARIES, FRACTURED TOOTH)
Treatment: ADVANCED RESTORATIVE (I.E., BASIC CROWNS)
HCPCS: D2710,D2712,D2751,D2752

Line: 467
Condition: GONADAL DYSFUNCTION, MENOPAUSAL MANAGEMENT (See Guideline Notes 64,65,74,88)
Treatment: OOPHORECTOMY, ORCHIECTOMY, HORMONAL REPLACEMENT FOR PURPOSES OTHER THAN INFERTILITY
ICD-10: E28.1-E28.2,E28.310-E28.9,E29.0-E29.9,E30.0,E34.50-E34.52,E89.40-E89.5,N50.0,N83.311-N83.319,N83.331-N83.339,N95.0-N95.9,N98.1,Q50.01-Q50.39,Q55.4,Q96.0-Q96.8,Q98.0-Q98.4,Z79.890
CPT: 54520,54660,54690,58300,58301,58660-58662,58740,58940,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9558

Line: 468
Condition: ENCOPRESIS NOT DUE TO A PHYSIOLOGICAL CONDITION (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F98.1
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0038,H0045,H2010,H2012-H2014,H2021,H2022,H2027,H2032,S5151,S9125,S9484,T1005

Line: 469
Condition: ACQUIRED PTOSIS AND OTHER EYELID DISORDERS WITH VISION IMPAIRMENT (See Guideline Notes 64,65,130)
Treatment: PTOSIS REPAIR
ICD-10: G90.2,H02.201-H02.519,H02.531-H02.539,Q10.0-Q10.3
CPT: 15822,15823,67710,67875-67912,67917,67961,67971,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Funding Level as of January 1, 2018

Line: **470**
Condition: KERATOCONJUNCTIVITIS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: A18.52,B60.12-B60.13,H16.101-H16.229,H16.251-H16.9,H18.461-H18.469,M35.01
CPT: 67515,67880,67882,68200,68760,68761,68801-68840,92002-92014,92018-92060,92081-92136,92225,92226,92230-92310,92325-92342,92370,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **471**
Condition: SELECTIVE MUTISM (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F94.0
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0023,H0032-H0038,H2010,H2012,H2014,H2021,H2022,H2027,H2032,H2033,S9484

Line: **472**
Condition: THROMBOSED AND COMPLICATED HEMORRHOIDS (See Guideline Notes 64,65)
Treatment: HEMORRHOIDECTOMY, INCISION
ICD-10: K64.3,K64.5
CPT: 44391,45317,45320,45334,45335,45350,45381,45382,45398,46083,46220,46221,46250-46262,46320,46500,46610-46615,46930,46945-46947,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **473**
Condition: CHRONIC OTITIS MEDIA; OPEN WOUND OF EAR DRUM (See Guideline Notes 51,64,65,154)
Treatment: PE TUBES/ADENOIDECTOMY/TYMPANOPLASTY, MEDICAL THERAPY
ICD-10: H65.20-H65.33,H65.411-H65.93,H66.10-H66.23,H66.3X1-H66.3X9,H68.001-H68.009,H68.021-H68.139,H69.00-H69.03,H70.10-H70.13,H70.90-H70.93,H72.00-H72.13,H72.2X1-H72.93,H73.10-H73.13,H73.811-H73.93,H74.01-H74.09,H74.40-H74.43,H74.8X1-H74.93,H95.111-H95.119,H95.131-H95.199,S09.20XA-S09.20XD,S09.21XA-S09.21XD,S09.22XA-S09.22XD
CPT: 42830-42836,69209-69222,69310,69420,69421,69433-69511,69601-69650,69700,69801,69905,69910,69979,92562-92565,92571-92577,92590,92591,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **474**
Condition: OTOSCLEROSIS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: H80.00-H80.93
CPT: 69650-69662,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **475**
Condition: FOREIGN BODY IN EAR AND NOSE (See Guideline Notes 64,65)
Treatment: REMOVAL OF FOREIGN BODY
ICD-10: T16.1XXA-T16.1XXD,T16.2XXA-T16.2XXD,T16.9XXA-T16.9XXD,T17.0XXA-T17.0XXD,T17.1XXA-T17.1XXD
CPT: 30300-30320,69200,69205,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **476**
Condition: CLOSED DISLOCATIONS/FRACTURES OF NON-CERVICAL VERTEBRAL COLUMN WITHOUT NEUROLOGIC INJURY OR STRUCTURAL INSTABILITY (See Guideline Notes 6,64,65,100,109,136)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: M43.5X4-M43.5X9,M48.40XA-M48.40XG,M48.43XA-M48.43XG,M48.44XA-M48.44XG,M48.45XA-M48.45XG,M48.46XA-M48.46XG,M48.47XA-M48.47XG,M48.48XA-M48.48XG,M48.50XA-M48.50XG,M48.53XA-M48.53XG,M48.54XA-M48.54XG,M48.55XA-M48.55XG,M48.56XA-M48.56XG,M48.57XA-M48.57XG,M48.58XA-M48.58XG,M80.08XA-M80.08XG,M80.88XA-M80.88XG,M84.58XA,M84.68XA,S22.000A,S22.000D-S22.000G,S22.001A,S22.001D-S22.001G,S22.002A,S22.002D-S22.002G,S22.008A,S22.008D-S22.008G,S22.009A,S22.009D-S22.009G,S22.010A,S22.010D-S22.010G,S22.011A,S22.011D-S22.011G,S22.012A,S22.012D-S22.012G,S22.018A,S22.018D-S22.018G,S22.019A,S22.019D-S22.019G,S22.020A,S22.020D-S22.020G,S22.021A,S22.021D-S22.021G,S22.022A,S22.022D-S22.022G,S22.028A,S22.028D-S22.028G,S22.029A,S22.029D-

S22.029G,S22.030A,S22.030D-S22.030G,S22.031A,S22.031D-S22.031G,S22.032A,S22.032D-S22.032G,S22.038A,S22.038D-S22.038G,S22.039A,S22.039D-S22.039G,S22.040A,S22.040D-S22.040G,S22.041A,S22.041D-S22.041G,S22.042A,S22.042D-S22.042G,S22.048A,S22.048D-S22.048G,S22.049A,S22.049D-S22.049G,S22.050A,S22.050D-S22.050G,S22.051A,S22.051D-S22.051G,S22.052A,S22.052D-S22.052G,S22.058A,S22.058D-S22.058G,S22.059A,S22.059D-S22.059G,S22.060A,S22.060D-S22.060G,S22.061A,S22.061D-S22.061G,S22.062A,S22.062D-S22.062G,S22.068A,S22.068D-S22.068G,S22.069A,S22.069D-S22.069G,S22.070A,S22.070D-S22.070G,S22.071A,S22.071D-S22.071G,S22.072A,S22.072D-S22.072G,S22.078A,S22.078D-S22.078G,S22.079A,S22.079D-S22.079G,S22.080A,S22.080D-S22.080G,S22.081A,S22.081D-S22.081G,S22.082A,S22.082D-S22.082G,S22.088A,S22.088D-S22.088G,S22.089A,S22.089D-S22.089G,S22.9XXA,S23.101A-S23.101D,S23.111A-S23.111D,S23.121A-S23.121D,S23.123A-S23.123D,S23.131A-S23.131D,S23.133A-S23.133D,S23.141A-S23.141D,S23.143A-S23.143D,S23.151A-S23.151D,S23.153A-S23.153D,S23.161A-S23.161D,S23.163A-S23.163D,S23.171A-S23.171D,S23.20XA-S23.20XD,S23.29XA-S23.29XD,S32.000A,S32.000D-S32.000G,S32.001A,S32.001D-S32.001G,S32.008A,S32.008D-S32.008G,S32.009A,S32.009D-S32.009G,S32.010A,S32.010D-S32.010G,S32.011A,S32.011D-S32.011G,S32.018A,S32.018D-S32.018G,S32.019A,S32.019D-S32.019G,S32.020A,S32.020D-S32.020G,S32.021A,S32.021D-S32.021G,S32.028A,S32.028D-S32.028G,S32.029A,S32.029D-S32.029G,S32.030A,S32.030D-S32.030G,S32.031A,S32.031D-S32.031G,S32.038A,S32.038D-S32.038G,S32.039A,S32.039D-S32.039G,S32.040A,S32.040D-S32.040G,S32.041A,S32.041D-S32.041G,S32.048A,S32.048D-S32.048G,S32.049A,S32.049D-S32.049G,S32.050A,S32.050D-S32.050G,S32.051A,S32.051D-S32.051G,S32.058A,S32.058D-S32.058G,S32.059A,S32.059D-S32.059G,S32.10XA,S32.10XD-S32.10XG,S32.110A,S32.110D-S32.110G,S32.111A,S32.111D-S32.111G,S32.112A,S32.112D-S32.112G,S32.119A,S32.119D-S32.119G,S32.120A,S32.120D-S32.120G,S32.121A,S32.121D-S32.121G,S32.122A,S32.122D-S32.122G,S32.129A,S32.129D-S32.129G,S32.130A,S32.130D-S32.130G,S32.131A,S32.131D-S32.131G,S32.132A,S32.132D-S32.132G,S32.139A,S32.139D-S32.139G,S32.14XA,S32.14XD-S32.14XG,S32.15XA,S32.15XD-S32.15XG,S32.16XA,S32.16XD-S32.16XG,S32.17XA,S32.17XD-S32.17XG,S32.19XA,S32.19XD-S32.19XG,S33.101A-S33.101D,S33.111A-S33.111D,S33.121A-S33.121D,S33.131A-S33.131D,S33.141A-S33.141D,S33.2XXA-S33.2XXD,S33.39XA-S33.39XD,Z47.2

CPT: 20930-20938,22310,22325-22328,22510-22819,22840-22855,22859,27216,27218,29035-29046,29700,29710,29720,63001-63011,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **477**
Condition: CONDUCT DISORDER, AGE 18 OR UNDER (See Guideline Notes 54,64,65,152)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F91.0-F91.2,F91.8-F91.9
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0034,H0036-H0039,H0045,H2010,H2012,H2014,H2021-H2023,H2027,H2032,H2033,S5151,S9125,S9480,S9484,T1005

Line: **478**
Condition: BREAST CYSTS AND OTHER DISORDERS OF THE BREAST (See Guideline Notes 64,65,149)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: N60.01-N60.99,N64.0,N64.89
CPT: 10160,19000,19001,19110-19126,49185,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **479**
Condition: CYSTS OF BARTHOLIN'S GLAND AND VULVA (See Guideline Notes 64,65)
Treatment: INCISION AND DRAINAGE, MEDICAL THERAPY
ICD-10: N75.0,N75.8-N75.9,N76.5-N76.6,N76.81-N76.89,N77.0
CPT: 10060,10061,11004,56440,56501,56515,56740,57135,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **480**
Condition: LICHEN PLANUS (See Guideline Notes 21,64,65)
Treatment: MEDICAL THERAPY
ICD-10: L43.0-L43.9,L44.1-L44.3,L66.1
CPT: 11900,11901,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **481**
Condition: RUPTURE OF SYNOVIUM
Treatment: REMOVAL OF BAKER'S CYST
ICD-10: M66.0,M71.20-M71.22
CPT: 27345,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **482**
Condition: ENOPHTHALMOS (See Guideline Notes 64,65)
Treatment: ORBITAL IMPLANT
ICD-10: H05.401-H05.429,H11.241-H11.249
CPT: 21076,21077,67550,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: D5915,D5928,D5992,D5993,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **483**
Condition: BELL'S PALSY, EXPOSURE KERATOCONJUNCTIVITIS (See Guideline Notes 64,65)
Treatment: TARSORRHAPHY
ICD-10: G51.0-G51.9,H02.59,H02.89,H16.211-H16.219
CPT: 15840-15842,64864-64868,67875-67882,67911,67917,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **484**
Condition: PERIPHERAL ENTHESOPATHIES (See Guideline Notes 6,64,65)
Treatment: MEDICAL THERAPY
ICD-10: M25.70,M25.721-M25.749,M25.761-M25.776,M46.00-M46.09,M60.10,M60.111-M60.19,M70.10-M70.52,M75.20-M75.22,M76.40-M76.72,M76.811-M76.9,M77.00-M77.9,Z45.42
CPT: 93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **485**
Condition: ANGIOEDEMA (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: D81.810,T78.3XXA-T78.3XXD
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **486**
Condition: CLOSED FRACTURE OF ONE OR MORE PHALANGES OF THE FOOT, NOT INCLUDING THE GREAT TOE
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: M84.377A-M84.377G,M84.378A-M84.378G,M84.379A-M84.379G,M84.477A-M84.477G,M84.478A-M84.478G,M84.479A-M84.479G,S92.501A,S92.501D-S92.501G,S92.502A,S92.502D-S92.502G,S92.503A,S92.503D-S92.503G,S92.504A,S92.504D-S92.504G,S92.505A,S92.505D-S92.505G,S92.506A,S92.506D-S92.506G,S92.511A,S92.511D-S92.511G,S92.512A,S92.512D-S92.512G,S92.513A,S92.513D-S92.513G,S92.514A,S92.514D-S92.514G,S92.515A,S92.515D-S92.515G,S92.516A,S92.516D-S92.516G,S92.521A,S92.521D-S92.521G,S92.522A,S92.522D-S92.522G,S92.523A,S92.523D-S92.523G,S92.524A,S92.524D-S92.524G,S92.525A,S92.525D-S92.525G,S92.526A,S92.526D-S92.526G,S92.531A,S92.531D-S92.531G,S92.532A,S92.532D-S92.532G,S92.533A,S92.533D-S92.533G,S92.534A,S92.534D-S92.534G,S92.535A,S92.535D-S92.535G,S92.536A,S92.536D-S92.536G,S92.591A,S92.591D-S92.591G,S92.592A,S92.592D-S92.592G,S92.599A,S92.599D-S92.599G,S92.901G,S92.902G,S92.909G,S92.911A,S92.911D-S92.911G,S92.912A,S92.912D-S92.912G,S92.919A,S92.919D-S92.919G,S99.201A,S99.201D-S99.201G,S99.202A,S99.202D-S99.202G,S99.209A,S99.209D-S99.209G,S99.211A,S99.211D-S99.211G,S99.212A,S99.212D-S99.212G,S99.219A,S99.219D-S99.219G,S99.221A,S99.221D-S99.221G,S99.222A,S99.222D-S99.222G,S99.229A,S99.229D-S99.229G,S99.231A,S99.231D-S99.231G,S99.232A,S99.232D-S99.232G,S99.239A,S99.239D-S99.239G,S99.241A,S99.241D-S99.241G,S99.242A,S99.242D-S99.242G,S99.249A,S99.249D-S99.249G,S99.291A,S99.291D-S99.291G,S99.292A,S99.292D-S99.292G,S99.299A,S99.299D-S99.299G
CPT: 28510,28515,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **487**
Condition: DERMATOPHYTOSIS OF NAIL, GROIN, AND FOOT AND OTHER DERMATOMYCOSIS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: B35.1,B35.3,B35.6-B35.8,B36.1-B36.9,B47.9,L08.1
CPT: 11720-11732,11750,93792,93793,96900,96902,96910-96913,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **488**
Condition: CLOSED FRACTURES OF RIBS, STERNUM AND COCCYX (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: M84.38XD-M84.38XG,M84.48XD-M84.48XG,M84.68XD-M84.68XG,S22.20XA,S22.20XD-S22.20XG,S22.21XA,S22.21XD-S22.21XG,S22.22XA,S22.22XD-S22.22XG,S22.23XA,S22.23XD-S22.23XG,S22.24XA,S22.24XD-S22.24XG,S22.31XA,S22.31XD-S22.31XG,S22.32XA,S22.32XD-S22.32XG,S22.39XA,S22.39XD-S22.39XG,S22.41XA,S22.41XD-S22.41XG,S22.42XA,S22.42XD-S22.42XG,S22.43XA,S22.43XD-S22.43XG,S22.49XA,S22.49XD-S22.49XG,S22.5XXA,S22.5XXD-S22.5XXG,S22.9XXD-S22.9XXG,S32.2XXA-S32.2XXG
CPT: 21820,27200,29200,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **489**
Condition: SPASTIC DIPLEGIA (See Guideline Note 170)
Treatment: RHIZOTOMY
ICD-10: G80.1,Z45.49
CPT: 21720,21725,62320-62323,62350-62370,63185,63190,63295,93792,93793,95990,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **490**
Condition: DENTAL CONDITIONS (E.G., PERIODONTAL DISEASE)
Treatment: ADVANCED PERIODONTICS (E.G., SURGICAL PROCEDURES AND SPLINTING)
HCPCS: D4240-D4245,D4260,D4261,D4268-D4321,D4381,D5982

Line: **491**
Condition: HEPATORENAL SYNDROME (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: K76.7
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **492**
Condition: PARAPHILIAS AND OTHER PSYCHOSEXUAL DISORDERS (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F65.0-F65.4,F65.50-F65.9,F66
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0023,H0032,H0034,H0035,H2010,H2014,H2027,H2032,H2033,S9484

Line: **493**
Condition: ECTROPION AND BENIGN NEOPLASM OF EYE
Treatment: ECTROPION REPAIR
ICD-10: D22.10-D22.12,D23.10-D23.12,D31.00-D31.92,H02.101-H02.149,H02.871-H02.879,H11.231-H11.239
CPT: 21280,21282,67343,67700-67808,67820-67850,67880,67882,67914-67924,67950-67975,68110-68135,68320-68340,68362,68705,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **494**
Condition: RAYNAUD'S SYNDROME (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: I73.00,I73.89-I73.9
CPT: 64821-64823,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378, 99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **495**
Condition: CALCIUM PYROPHOSPHATE DEPOSITION DISEASE (CPPD) AND HYDROXYAPETITE DEPOSITION DISEASE (See Guideline Notes 6,64,65)
Treatment: MEDICAL THERAPY
ICD-10: M11.00,M11.011-M11.09,M11.20,M11.211-M11.89
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0511,G0513,G0514,S9152

Line: **496**
Condition: PHIMOSIS
Treatment: SURGICAL TREATMENT
ICD-10: N47.0-N47.1,N47.5
CPT: 54150-54161,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **497**
Condition: CERUMEN IMPACTION (See Guideline Notes 64,65)
Treatment: REMOVAL OF EAR WAX
ICD-10: H61.20-H61.23
CPT: 69209,69210,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378, 99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **498**
Condition: SIALOLITHIASIS, MUCOCELE, DISTURBANCE OF SALIVARY SECRETION, OTHER AND UNSPECIFIED DISEASES OF SALIVARY GLANDS (See Guideline Notes 64,65,128)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: K11.5-K11.9,R68.2
CPT: 40810-40816,42300,42305,42330-42340,42408-42425,42440-42510,42600-42665,64611,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480, 99487-99490,99495-99498,99605-99607
HCPCS: D7979-D7982,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513,G0514

Line: **499**
Condition: CHRONIC CONJUNCTIVITIS, BLEPHAROCONJUNCTIVITIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: E50.6,H02.721-H02.729,H10.401-H10.409,H10.421-H10.44,H10.501-H10.9,H11.141-H11.149,H11.421-H11.429, H16.261-H16.269
CPT: 92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060, 99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498, 99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **500**
Condition: CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS (See Guideline Notes 64,65,172)
Treatment: SPECIFIED INTERVENTIONS

Line: **501**
Condition: OTHER DISORDERS OF SYNOVIUM, TENDON AND BURSA, COSTOCHONDRITIS, AND CHONDRODYSTROPHY (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: M65.20,M65.221-M65.29,M66.10,M66.20,M66.9,M67.90,M67.911-M67.99,M70.031-M70.12,M70.31-M70.32, M70.41-M70.42,M71.10,M71.111-M71.19,M71.40,M71.421-M71.58,M71.9,M85.30,M85.311-M85.39,M89.00, M89.011-M89.09,M89.611-M89.69,M90.811-M90.89,M94.0-M94.1,M94.351-M94.8X9,Q77.8-Q77.9,Q78.4,Q78.8-Q78.9
CPT: 20550-20553,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378, 99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **502**
Condition: ERYTHEMATOUS CONDITIONS (See Guideline Notes 21,64,65)
Treatment: MEDICAL THERAPY
ICD-10: H01.121-H01.129,L26,L30.4,L49.0-L49.6,L49.8-L49.9,L51.0,L51.8-L51.9,L52,L53.0-L53.9,L54,L71.0,L92.0,L93.0-L93.2,L95.1,L98.2
CPT: 17340,17360,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378, 99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **503**
Condition: PERIPHERAL ENTHESOPATHIES (See Guideline Note 28)
Treatment: SURGICAL TREATMENT
ICD-10: M25.70,M25.721-M25.749,M25.761-M25.776,M46.00-M46.09,M70.10-M70.72,M75.20-M75.22,M76.40-M76.72, M76.811-M76.9,M77.00-M77.9
CPT: 20550-20553,20600-20611,21032,23931,24105,24357-24359,25109,25447,26035,26060,26121-26180,26320, 26440-26556,26565-26596,26820-26863,27060,27062,27097,27100-27122,27140-27170,27306,27307,27448-27455,27466,27468,27475-27485,27715,27730-27742,28119,64702,64704,64718-64727,64774,64856,64857, 64872-64907,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **504**
Condition: NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES (See Guideline Notes 35,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: J33.0-J33.9,J34.1,J34.81-J34.9,Q30.8,T70.1XXA-T70.1XXD
CPT: 30000,30020,30110-30140,30200-30420,30435,30450,30465-30930,31000-31230,31237-31298,61782,93792, 93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449, 99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **505**
Condition: DENTAL CONDITIONS (E.G., PULPAL PATHOLOGY, PERMANENT BICUSPID/PREMOLAR TOOTH)
Treatment: ADVANCED ENDODONTICS (E.G., RETREATMENT OF PREVIOUS ROOT CANAL THERAPY)
HCPCS: D3331,D3333,D3347,D3421,D3426,D3430,D3450

Line: **506**
Condition: CIRCUMSCRIBED SCLERODERMA (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: L94.0-L94.1,L94.3
CPT: 11900,11901,17000-17004,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285, 99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **507**
Condition: PERIPHERAL NERVE DISORDERS (See Guideline Notes 6,64,65,133)
Treatment: MEDICAL THERAPY
ICD-10: G13.0,G54.0-G54.9,G55,G56.10-G56.13,G56.30-G56.93,G57.00-G57.23,G57.70-G57.93,G58.0-G58.9,G59, G61.1,G61.81-G61.89,G62.0-G62.2,G62.81-G62.89,G63-G64,M53.0,S44.00XA-S44.00XD,S44.01XA-S44.01XD, S44.02XA-S44.02XD,S44.10XA-S44.10XD,S44.11XA-S44.11XD,S44.12XA-S44.12XD,S44.20XA-S44.20XD, S44.21XA-S44.21XD,S44.22XA-S44.22XD,S44.30XA-S44.30XD,S44.31XA-S44.31XD,S44.32XA-S44.32XD, S44.40XA-S44.40XD,S44.41XA-S44.41XD,S44.42XA-S44.42XD,S54.00XA-S54.00XD,S54.01XA-S54.01XD, S54.02XA-S54.02XD,S54.10XA-S54.10XD,S54.11XA-S54.11XD,S54.12XA-S54.12XD,S54.20XA-S54.20XD, S54.21XA-S54.21XD,S54.22XA-S54.22XD,S64.00XA-S64.00XD,S64.01XA-S64.01XD,S64.02XA-S64.02XD, S64.10XA-S64.10XD,S64.11XA-S64.11XD,S64.12XA-S64.12XD,S64.20XA-S64.20XD,S64.21XA-S64.21XD, S64.22XA-S64.22XD,S64.30XA-S64.30XD,S64.31XA-S64.31XD,S64.32XA-S64.32XD,S64.40XA-S64.40XD, S64.490A-S64.490D,S64.491A-S64.491D,S64.492A-S64.492D,S64.493A-S64.493D,S64.494A-S64.494D,

S64.495A-S64.495D,S64.496A-S64.496D,S64.497A-S64.497D,S64.498A-S64.498D,S74.00XA-S74.00XD, S74.01XA-S74.01XD,S74.02XA-S74.02XD,S74.10XA-S74.10XD,S74.11XA-S74.11XD,S74.12XA-S74.12XD, S94.00XA-S94.00XD,S94.01XA-S94.01XD,S94.02XA-S94.02XD,S94.10XA-S94.10XD,S94.11XA-S94.11XD, S94.12XA-S94.12XD,S94.20XA-S94.20XD,S94.21XA-S94.21XD,S94.22XA-S94.22XD

CPT: 90284,93792,93793,97110,97112,97116,97124,97161-97168,97530,98966-98969,99051,99060,99070,99078, 99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **508**
Condition: DYSFUNCTION OF NASOLACRIMAL SYSTEM IN ADULTS; LACRIMAL SYSTEM LACERATION (See Guideline Notes 64,65,134)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: H04.001-H04.9,M35.00,P39.1,Q10.6-Q10.7
CPT: 67880,67882,68420,68520,68530,68720-68840,92002-92014,92018-92060,92071,93792,93793,98966-98969, 99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **509**
Condition: BENIGN NEOPLASM OF KIDNEY AND OTHER URINARY ORGANS (See Guideline Notes 64,65,96)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: D17.71,D30.00-D30.9,D3A.093
CPT: 50542,50543,50545,50546,50562,52224,52282,53260,53265,93792,93793,98966-98969,99051,99060,99070, 99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498, 99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **510**
Condition: VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: H81.10-H81.23,H81.311-H81.93,H82.1-H82.9,H83.11-H83.19,H83.2X1-H83.2X9,H83.8X1-H83.93,T75.3XXA-T75.3XXD
CPT: 69666,69667,69805,69806,69915,69950,92531-92548,93792,93793,95992,98966-98969,99051,99060,99070, 99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498, 99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **511**
Condition: ESOPHAGITIS AND GERD; ESOPHAGEAL SPASM; ASYMPTOMATIC DIAPHRAGMATIC HERNIA (See Guideline Notes 64,65,144)
Treatment: MEDICAL THERAPY
ICD-10: K20.8-K20.9,K21.0-K21.9,K22.10,K22.5,K44.9,T17.218A-T17.218D,T17.318A-T17.318D,T18.118A-T18.118D
CPT: 43180,43229,43248,43249,43255,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **512**
Condition: HIDRADENITIS SUPPURATIVA; DISSECTING CELLULITIS OF THE SCALP
Treatment: MEDICAL THERAPY
ICD-10: L66.2-L66.3,L66.8-L66.9,L73.2
CPT: 11000,11001,11450-11471,11900,11901,64650,64653,93792,93793,98966-98969,99051,99060,99070,99078, 99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **513**
Condition: CHRONIC PROSTATITIS, OTHER DISORDERS OF PROSTATE (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: N41.1,N41.3,N41.9,N42.0-N42.1,N42.30-N42.9
CPT: 55801,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404, 99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **514**
Condition: PHLEBITIS AND THROMBOPHLEBITIS, SUPERFICIAL (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: I80.00-I80.03,I80.3-I80.9,I82.711-I82.719,I82.811-I82.819,I83.10-I83.12,I87.021-I87.029,I87.321-I87.329,Z79.01
CPT: 29584,36465,36466,36470-36479,37500,37700-37785,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **515**
Condition: DISORDERS OF SWEAT GLANDS (See Coding Specification Below) (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: L30.1,L74.0-L74.4,L74.510-L74.9,L75.0-L75.9,R61
CPT: 11450-11471,64650,64653,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Chemodenervation with botulinum toxin injection (CPT 64650, 64653) is included on this line for the treatment of axillary hyperhidrosis and palmar hyperhidrosis (ICD-10 L74.52, R61)

Line: **516**
Condition: PARALYSIS OF VOCAL CORDS OR LARYNX (See Guideline Notes 64,65,141)
Treatment: INCISION/EXCISION/ENDOSCOPY
ICD-10: J38.00-J38.02,J38.6
CPT: 31513,31551-31554,31570,31571,31574,31590,31591,92507,92508,92524,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **517**
Condition: POSTTHROMBOTIC SYNDROME
Treatment: MEDICAL THERAPY
ICD-10: I87.001-I87.009,I87.021-I87.029,I87.091-I87.099
CPT: 29584,36465-36479,37700-37761,37766-37790,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **518**
Condition: FOREIGN BODY IN GASTROINTESTINAL TRACT WITHOUT RISK OF PERFORATION OR OBSTRUCTION
Treatment: MEDICAL THERAPY
ICD-10: T18.2XXA-T18.2XXD,T18.3XXA-T18.3XXD,T18.4XXA-T18.4XXD,T18.5XXA-T18.5XXD,T18.8XXA-T18.8XXD,T18.9XXA-T18.9XXD
CPT: 43247,44363,44390,45307,45332,45379,45915,46608,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **519**
Condition: PANNICULITIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: M35.6,M79.3
CPT: 68760,68761,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **520**
Condition: ROSACEA; ACNE (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: L70.0-L70.9,L71.1-L71.9,L73.0
CPT: 10040-10061,11900,11901,17000,17340,17360,93792,93793,96900,96902,96910-96913,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **521**
Condition: SEXUAL DYSFUNCTION (See Guideline Notes 64,65,159)
Treatment: PSYCHOTHERAPY, MEDICAL AND SURGICAL TREATMENT
ICD-10: F10.181,F10.281,F10.981,F11.181,F11.281,F11.981,F12.188,F12.288,F12.988,F13.181,F13.281,F13.981,F14.181,F14.281,F14.981,F15.181,F15.281,F15.981,F19.181,F19.281,F19.981,F52.0-F52.1,F52.21-F52.4,F52.6-F52.9,N52.01-N52.9,N53.11-N53.19,R37
CPT: 54235,54400-54417,90785,90832-90840,90846-90853,90882,90887,93792,93793,93980,93981,98966-98969,99051,99060,99070,99078,99201-99239,99281-99285,99291-99366,99374,99375,99379-99404,99408-99449,99471-99476,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0490,G0508-G0511,G0513,G0514,H0004,H0023,H0032-H0035,H0038,H2014,H2027,H2032,S9484

Line: **522**
Condition: UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER OR DIAPHRAGMATIC HERNIA) (See Guideline Notes 24,64,65)
Treatment: REPAIR
ICD-10: K40.20-K40.21,K40.90-K40.91,K41.20-K41.21,K41.90-K41.91,K42.9,K43.2,K43.5,K43.9,K45.8,K46.9
CPT: 44050,49250,49505,49520,49525-49550,49555,49560,49565,49568,49570,49580,49585,49590,49650-49659,55540,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **523**
Condition: BENIGN NEOPLASM OF NASAL CAVITIES, MIDDLE EAR AND ACCESSORY SINUSES
Treatment: EXCISION, RECONSTRUCTION
ICD-10: D14.0
CPT: 30117-30150,30520,31020,31032,31201,61782,69145,69501-69554,69960,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **524**
Condition: CHRONIC ANAL FISSURE (See Guideline Notes 52,64,65)
Treatment: SPHINCTEROTOMY, FISSURECTOMY, FISTULECTOMY, MEDICAL THERAPY
ICD-10: K60.1-K60.2
CPT: 45905,45910,46020,46030,46080,46200,46270-46288,46505,46700,46706,46707,46940,46942,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **525**
Condition: DEFORMITIES OF UPPER BODY AND ALL LIMBS (See Guideline Notes 64,65,94)
Treatment: REPAIR/REVISION/RECONSTRUCTION/RELOCATION/MEDICAL THERAPY
ICD-10: M20.001-M20.099,M21.00,M21.021-M21.079,M21.121-M21.169,M21.20,M21.211-M21.279,M21.371-M21.379,M21.519-M21.529,M21.70,M21.721-M21.959,M24.031-M24.059,M24.121-M24.159,M24.444-M24.446,M24.621-M24.659,M24.7,M24.821-M24.859,M25.10,M25.111-M25.18,M25.221-M25.269,M25.28,M25.321-M25.369,M25.80,M25.811-M25.869,M72.1,M72.4,M85.9,M89.121-M89.29,M89.70,M89.711-M89.79,M89.9,M92.00-M92.12,M92.201-M92.32,M92.8-M92.9,M93.1,M93.80,M93.811-M93.99,M94.9,M95.5-M95.8,M99.85-M99.87,M99.89,Q65.9,Q67.6,Q68.1-Q68.5,Q68.8,Q72.70,Q74.0-Q74.9,Q76.6-Q76.9,Q79.6-Q79.8
CPT: 11042,11045,20150,20690-20694,21740-21743,24000,24006,24101,24102,25101-25109,25320,25335,25337,25390-25393,25441-25492,25810-25830,26035,26055,26060,26121-26180,26320,26390,26426,26432,26440-26556,26565-26596,26820-26863,27097,27100-27122,27140,27185,27306,27307,27435,27448-27455,27465-27468,27475-27485,27590,27656,27676,27685-27690,27705,27715,27727-27742,28300,28304,29075,29130,29345,29540,29861-29863,64702,64704,64718-64727,64774-64783,64788-64792,64856,64857,64872-64907,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **526**
Condition: DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS (See Guideline Notes 64,65,129)
Treatment: MEDICAL AND SURGICAL THERAPY
ICD-10: D78.02,G43.A0-G43.A1,G43.D0-G43.D1,K30,K31.0,K31.2,K31.4,K31.83-K31.9,K58.0-K58.9,K59.00-K59.1,K59.4-K59.9,K91.0-K91.1,K91.89,P78.3,R15.0,R15.2-R15.9
CPT: 44141-44144,44188,44206,44320,44340-44346,45110,45395,45397,46761,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 527
Condition: CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS (See Guideline Notes 37,60,64,65,100,101,161)
Treatment: SURGICAL THERAPY
ICD-10: G95.0,M40.00-M40.15,M40.202-M40.57,M42.00-M42.9,M43.00-M43.28,M43.8X1-M43.8X9,M45.0-M45.9,M46.1, M46.40-M46.99,M47.20-M47.28,M47.811-M47.9,M48.00-M48.05,M48.061-M48.19,M48.30-M48.38,M48.8X1-M48.9,M49.80-M49.89,M50.10-M50.11,M50.120-M50.93,M51.14-M51.9,M53.80-M53.9,M54.10-M54.18,M96.1-M96.4,M99.20-M99.79,Q06.0-Q06.3,Q06.8-Q06.9,Q76.0-Q76.2,Q76.411-Q76.49,S13.0XXA-S13.0XXD, S23.0XXA-S23.0XXD,S23.100A-S23.100D,S23.110A-S23.110D,S23.120A-S23.120D,S23.122A-S23.122D, S23.130A-S23.130D,S23.132A-S23.132D,S23.140A-S23.140D,S23.142A-S23.142D,S23.150A-S23.150D, S23.152A-S23.152D,S23.160A-S23.160D,S23.162A-S23.162D,S23.170A-S23.170D,S33.0XXA-S33.0XXD, S33.100A-S33.100D,S33.110A-S33.110D,S33.120A-S33.120D,S33.130A-S33.130D,S33.140A-S33.140D, S34.3XXA-S34.3XXD
CPT: 20610,20660-20665,20930-20938,21720,21725,22206-22226,22532-22865,27035,27096,27279,29000-29046, 29710,29720,62287,62322,62323,63001-63091,63170,63173-63200,63270-63273,63295-63610,63650,63655, 63685,64483,64484,64493-64495,93792,93793,96150-96155,97110-97124,97140-97168,97530,97535,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480, 99487,99489,99495,99496,99605-99607
HCPCS: G0157-G0160,G0248-G0250,G0260,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0508-G0511, G0513,G0514,S2350,S2351

Line: 528
Condition: FIBROMYALGIA, CHRONIC FATIGUE SYNDROME, AND RELATED DISORDERS (See Guideline Notes 64,65,135)
Treatment: MEDICAL THERAPY
ICD-10: G89.21,G89.28-G89.29,G89.4,M79.7,R53.82
CPT: 90785,90832-90840,90846-90853,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: 529
Condition: CHRONIC PELVIC INFLAMMATORY DISEASE, PELVIC PAIN SYNDROME, DYSPAREUNIA (See Guideline Notes 55,64,65,110)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: N70.11-N70.93,N71.1-N71.9,N73.1-N73.2,N73.4-N73.9,N74,N83.8,N94.0,N94.10-N94.2,N94.810-N94.89,R10.2
CPT: 49322,58150,58180,58260,58262,58290,58291,58400,58410,58541-58544,58550-58554,58562,58570-58573, 58660-58662,58700-58740,58805,58925,58940,93792,93793,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 530
Condition: MILD ECZEMA (See Guideline Notes 21,64,65,156)
Treatment: MEDICAL THERAPY
ICD-10: E08.620,E09.620,E10.620,E11.620,E13.620,L20.0,L20.81-L20.9,Z51.6
CPT: 86003,86008,86486,93792,93793,95004,95018-95180,96900,96902,96910-96913,98966-98969,99051,99060, 99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498, 99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: 531
Condition: CONTACT DERMATITIS AND NON-INFECTIOUS OTITIS EXTERNA (See Guideline Notes 64,65,156)
Treatment: MEDICAL THERAPY
ICD-10: H60.501-H60.93,L23.0-L23.7,L23.81-L23.9,L24.0-L24.7,L24.81-L24.9,L25.0-L25.9,L30.0,L30.2,L30.8-L30.9,L56.0-L56.4,L56.8-L56.9,L57.1,L57.5-L57.9,L58.0-L58.9,L59.0-L59.9,Z51.6
CPT: 86003,86008,86486,93792,93793,95004,95018-95180,96900,96902,96910-96913,98966-98969,99051,99060, 99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498, 99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: 532
Condition: HYPOTENSION (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: G90.01,I95.0-I95.3,I95.81-I95.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **533**
Condition: VIRAL, SELF-LIMITING ENCEPHALITIS, MYELITIS AND ENCEPHALOMYELITIS (See Guideline Notes 61,64,65)
Treatment: MEDICAL THERAPY
ICD-10: A81.89-A81.9,A83.0-A83.9,A84.0-A84.9,A85.0-A85.1,A85.8,A86,B01.11-B01.12,B05.0,B06.00-B06.09,B06.82, G04.81-G04.91,G05.3-G05.4,G37.4
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **534**
Condition: PERIPHERAL NERVE DISORDERS (See Guideline Note 133)
Treatment: SURGICAL TREATMENT
ICD-10: G54.0-G54.4,G54.6-G54.9,G55,G56.10-G56.13,G56.30-G56.93,G57.00-G57.23,G57.70-G57.93,G58.0-G58.9, M53.0,S44.00XA-S44.00XD,S44.01XA-S44.01XD,S44.02XA-S44.02XD,S44.10XA-S44.10XD,S44.11XA-S44.11XD,S44.12XA-S44.12XD,S44.20XA-S44.20XD,S44.21XA-S44.21XD,S44.22XA-S44.22XD,S44.30XA-S44.30XD,S44.31XA-S44.31XD,S44.32XA-S44.32XD,S44.40XA-S44.40XD,S44.41XA-S44.41XD,S44.42XA-S44.42XD,S54.00XA-S54.00XD,S54.01XA-S54.01XD,S54.02XA-S54.02XD,S54.10XA-S54.10XD,S54.11XA-S54.11XD,S54.12XA-S54.12XD,S54.20XA-S54.20XD,S54.21XA-S54.21XD,S54.22XA-S54.22XD,S64.00XA-S64.00XD,S64.01XA-S64.01XD,S64.02XA-S64.02XD,S64.10XA-S64.10XD,S64.11XA-S64.11XD,S64.12XA-S64.12XD,S64.20XA-S64.20XD,S64.21XA-S64.21XD,S64.22XA-S64.22XD,S64.30XA-S64.30XD,S64.31XA-S64.31XD,S64.32XA-S64.32XD,S64.40XA-S64.40XD,S64.490A-S64.490D,S64.491A-S64.491D,S64.492A-S64.492D,S64.493A-S64.493D,S64.494A-S64.494D,S64.495A-S64.495D,S64.496A-S64.496D,S64.497A-S64.497D,S64.498A-S64.498D,S74.00XA-S74.00XD,S74.01XA-S74.01XD,S74.02XA-S74.02XD,S74.10XA-S74.10XD,S74.11XA-S74.11XD,S74.12XA-S74.12XD,S94.00XA-S94.00XD,S94.01XA-S94.01XD,S94.02XA-S94.02XD,S94.10XA-S94.10XD,S94.11XA-S94.11XD,S94.12XA-S94.12XD,S94.20XA-S94.20XD,S94.21XA-S94.21XD,S94.22XA-S94.22XD
CPT: 23397,64702-64719,64722-64727,64774-64792,64820,64856,64857,64872-64907,93792,93793,98966-98969, 99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **535**
Condition: DENTAL CONDITIONS (E.G., PULPAL PATHOLOGY, PERMANENT MOLAR TOOTH)
Treatment: ADVANCED ENDODONTICS (E.G., RETREATMENT OF PREVIOUS ROOT CANAL THERAPY)
HCPCS: D3331,D3333,D3348,D3425,D3426,D3430,D3450

Line: **536**
Condition: ICHTHYOSIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: Q80.0-Q80.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **537**
Condition: LESION OF PLANTAR NERVE; PLANTAR FASCIAL FIBROMATOSIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY, EXCISION
ICD-10: G57.60-G57.63,M72.2
CPT: 20550,28008,28060,28080,29893,64455,64632,64726,93792,93793,98966-98969,99051,99060,99070,99078, 99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **538**
Condition: TENSION HEADACHES (See Coding Specification Below) (See Guideline Notes 64,65,92)
Treatment: MEDICAL THERAPY
ICD-10: G44.201-G44.52,G44.59-G44.89,M99.80,R51
CPT: 93792,93793,97810-98942,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378, 99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Osteopathic manipulative treatment and chiropractic manipulative treatment (CPT 98926-98929, 98940- 98943) pair on this line only with cervicogenic headache (R51).

Line: **539**
Condition: MILD PSORIASIS; DERMATOPHYTOSIS: SCALP, HAND, BODY (See Guideline Notes 21,64,65)
Treatment: MEDICAL THERAPY
ICD-10: B35.0,B35.2,B35.4-B35.5,B35.9,L40.0-L40.4,L40.8-L40.9,L41.0-L41.9,L44.0,L94.5
CPT: 11900,11901,93792,93793,96900,96902,96910-96922,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **540**
Condition: DEFORMITIES OF FOOT (See Guideline Notes 64,65,158)
Treatment: FASCIOTOMY/INCISION/REPAIR/ARTHRODESIS
ICD-10: M20.10-M20.12,M20.30-M20.42,M20.5X1-M20.62,M21.171-M21.172,M21.531-M21.6X9,M21.961-M21.969,M24.074-M24.076,M24.477-M24.479,M24.674-M24.676,M24.873,M24.876,M25.271-M25.279,M25.371-M25.376,M92.60-M92.72,Q66.80-Q66.9,Q72.70,Q74.2
CPT: 27612,27690-27692,28008,28010,28035,28050-28072,28086-28092,28110-28119,28126-28160,28220-28289,28292-28341,28360,28705-28730,28737-28760,29405,29425,29450,29750,29904-29907,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **541**
Condition: FOREIGN BODY GRANULOMA OF MUSCLE, SKIN AND SUBCUTANEOUS TISSUE (See Guideline Notes 64,65)
Treatment: REMOVAL OF GRANULOMA
ICD-10: L92.3,M60.20,M60.211-M60.28
CPT: 21011-21014,21552-21556,21930-21933,22901-22903,23071-23076,24071-24076,25071-25076,26111-26116,27043-27048,27327,27328,27337,27339,27618,27619,27632,27634,28039-28045,28192,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **542**
Condition: HYDROCELE (See Guideline Notes 64,65,149)
Treatment: MEDICAL THERAPY, EXCISION
ICD-10: N43.3,N43.40-N43.42,N50.89,P83.5
CPT: 49185,54840,55000-55060,55500,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **543**
Condition: SYMPTOMATIC URTICARIA (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: L50.0-L50.1,L50.5-L50.8,T78.1XXA-T78.1XXD
CPT: 86003,86008,93792,93793,96900,96902,96910-96913,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **544**
Condition: IMPULSE DISORDERS (See Guideline Notes 58,64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F63.1-F63.2,F63.81-F63.9
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0034,H0036-H0039,H0045,H2010,H2013,H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9484,T1005

Line: **545**
Condition: SUBLINGUAL, SCROTAL, AND PELVIC VARICES (See Guideline Notes 64,65)
Treatment: VENOUS INJECTION, VASCULAR SURGERY
ICD-10: I86.0-I86.2
CPT: 36470,37241,37242,55530,55535,55550,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **546**
Condition: ASEPTIC MENINGITIS (See Guideline Notes 61,64,65)
Treatment: MEDICAL THERAPY
ICD-10: A87.0-A87.9,A88.0,A88.8,A89,B01.0,B05.1,G02,G03.2
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **547**
Condition: TMJ DISORDER (See Guideline Notes 64,65)
Treatment: TMJ SPLINTS
ICD-10: M26.601-M26.69,S03.40XA-S03.40XD,S03.41XA-S03.41XD,S03.42XA-S03.42XD,S03.43XA-S03.43XD
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: D7880,D7881,G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **548**
Condition: CHRONIC DISEASE OF TONSILS AND ADENOIDS (See Guideline Notes 36,64,65)
Treatment: TONSILLECTOMY AND ADENOIDECTOMY
ICD-10: J35.01-J35.9
CPT: 42820-42836,42860,42870,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **549**
Condition: SOMATIC SYMPTOMS AND RELATED DISORDERS (See Guideline Notes 64,65)
Treatment: CONSULTATION
ICD-10: F44.0-F44.7,F44.81-F44.9,F45.0-F45.1,F45.20-F45.9,F52.5,F68.10-F68.13
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,96150-96155,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0017,H0019,H0023,H0032-H0039,H2010,H2012-H2014,H2021-H2023,H2027,H2032,H2033,S9484

Line: **550**
Condition: OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS (See Guideline Notes 61,64,65,156)
Treatment: MEDICAL THERAPY
ICD-10: K52.1,K52.21-K52.29,K52.81-K52.82,K52.831-K52.9,K90.9,Z51.6
CPT: 86003,86008,86486,93792,93793,95004,95018-95180,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **551**
Condition: HEMATOMA OF AURICLE OR PINNA AND HEMATOMA OF EXTERNAL EAR (See Guideline Notes 64,65)
Treatment: DRAINAGE
ICD-10: H61.101-H61.199,H61.811-H61.899,M95.10-M95.12
CPT: 10140,69000-69020,69140,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **552**
Condition: OTHER HYPERTROPHIC OR ATROPHIC CONDITIONS OF SKIN (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: H01.111-H01.119,H01.131-H01.149,L11.0,L11.8-L11.9,L21.0-L21.9,L28.0-L28.2,L29.0-L29.9,L30.3,L57.2,L57.4,L66.4,L83,L85.0-L85.2,L85.8-L85.9,L86,L87.0-L87.9,L90.1-L90.4,L90.6-L90.9,L91.8-L91.9,L92.2,L94.8-L94.9,L98.1,L98.5-L98.6
CPT: 11000-11057,11200,11201,11401-11406,11900,11950-11954,17000-17004,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **553**
Condition: CHONDROMALACIA (See Guideline Notes 6,64,65)
Treatment: MEDICAL THERAPY
ICD-10: M94.20,M94.211-M94.29
CPT: 93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060, 99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498, 99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **554**
Condition: CYST OF KIDNEY, ACQUIRED (See Guideline Notes 64,65,149)
Treatment: MEDICAL THERAPY
ICD-10: N28.1
CPT: 49185,50390,50541,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285, 99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **555**
Condition: DYSMENORRHEA (See Guideline Notes 59,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: N94.4-N94.6
CPT: 58150,58180,58260,58290,58541-58544,58550-58554,58570-58573,93792,93793,98966-98969,99051,99060, 99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **556**
Condition: BENIGN NEOPLASM OF BONE AND ARTICULAR CARTILAGE INCLUDING OSTEOID OSTEOMAS; BENIGN NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE (See Guideline Notes 6,7,11,64,65,100,137)
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10: D16.00-D16.9,D17.79,D18.09,D21.0,D21.10-D21.9,D36.10-D36.17,D48.1,D61.810,G89.3,K09.0-K09.1,M12.20, M12.211-M12.29,M27.1,M27.40-M27.49,M27.8,M67.80,M67.811-M67.89,M85.00,M85.011-M85.09,M85.40, M85.411-M85.69,Z51.0,Z51.12
CPT: 11400-11446,12051,12052,13131,17106-17111,20150,20550,20551,20600-20611,20615,20930-20938,20955-20973,21011-21014,21025-21032,21040,21046-21049,21181,21198,21552-21556,21600,21930-21936,22532-22819,22853,22854,22859,23071-23076,23101-23106,23140-23156,23200,24071-24079,24102-24126,24420, 24498,25000,25071,25073,25105,25110-25136,25170-25240,25295-25301,25320,25335,25337,25390-25393, 25441-25447,25450-25492,25810-25830,26100-26116,26130,26200-26215,26250-26262,26449,27025,27043-27049,27054,27059,27065-27078,27187,27327,27328,27334-27339,27355-27358,27365,27465-27468,27495, 27625-27638,27645-27647,27656,27745,28039-28045,28070,28072,28100-28108,28122,28124,28171-28175, 28820,28825,29820,29821,29835,29836,29844,29845,29863,29875,29876,29895,29905,32553,36680,49411, 63081-63103,64774,64792,77014,77261-77295,77300-77307,77331-77338,77385-77387,77401-77427,77469, 77470,79005-79445,93792,93793,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,97012, 97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513,G0514,G6001-G6017

Line: **557**
Condition: SPASTIC DYSPHONIA (See Coding Specification Below) (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: J38.3
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514,S2340,S2341

ICD-10 J38.3 is included on Line 206 for treatment of abscesses and cellulitis of the vocal cords; it is included on Line 557 for treatment of spastic dysphonia.

Line: **558**
Condition: MACROMASTIA (See Guideline Note 166)
Treatment: BREAST REDUCTION
ICD-10: N62
CPT: 19318,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404, 99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **559**
Condition: ALLERGIC RHINITIS AND CONJUNCTIVITIS, CHRONIC RHINITIS (See Guideline Notes 64,65,156)
Treatment: MEDICAL THERAPY
ICD-10: H10.011-H10.239,H10.411-H10.419,H10.45,H11.111-H11.129,J30.0-J30.5,J30.81-J30.9,J31.0-J31.2,T78.40XA-T78.40XD,T78.49XA-T78.49XD,Z51.6
CPT: 30420,86003,86008,86486,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,95004,95018-95180,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **560**
Condition: CANCER OF LIVER AND INTRAHEPATIC BILE DUCTS
Treatment: LIVER TRANSPLANT
ICD-10: C22.0-C22.8,T86.40-T86.49,Z48.23,Z51.11,Z52.6
CPT: 47133-47147,86825-86835,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **561**
Condition: BENIGN NEOPLASM AND CONDITIONS OF EXTERNAL FEMALE GENITAL ORGANS
Treatment: EXCISION
ICD-10: D28.0-D28.1,D28.7-D28.9,I86.3,N89.9
CPT: 56440,56441,56501,57130,57135,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **562**
Condition: HORDEOLUM AND OTHER DEEP INFLAMMATION OF EYELID; CHALAZION (See Guideline Notes 64,65)
Treatment: INCISION AND DRAINAGE, MEDICAL THERAPY
ICD-10: H00.011-H00.029,H00.11-H00.19,H02.70,H02.79,H02.821-H02.829,H02.861-H02.869
CPT: 67700,67800-67808,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **563**
Condition: ACUTE ANAL FISSURE (See Guideline Notes 64,65)
Treatment: FISSURECTOMY, MEDICAL THERAPY
ICD-10: K60.0
CPT: 46200,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **564**
Condition: PLEURISY (See Guideline Notes 64,65,149)
Treatment: MEDICAL THERAPY
ICD-10: J92.0-J92.9,J94.1,J94.8-J94.9,R09.1
CPT: 32200-32310,32550,32552,32560-32562,32650-32652,32655,32664,32665,32940,49185,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **565**
Condition: PERITONEAL ADHESION
Treatment: SURGICAL TREATMENT
ICD-10: K66.0,K66.8-K66.9,K68.9,N99.4
CPT: 44005,44180,44603,44604,49423,58660-58662,58740,58940,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **566**
Condition: DERMATITIS DUE TO SUBSTANCES TAKEN INTERNALLY (See Guideline Notes 64,65,156)
Treatment: MEDICAL THERAPY
ICD-10: L27.1-L27.9,Z51.6
CPT: 86003,86008,86486,93792,93793,95004,95018-95180,98966-98969,99051,99060,99070,99078,99201-99215, 99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **567**
Condition: BLEPHARITIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: H01.001-H01.029,H01.8-H01.9,H02.831-H02.839
CPT: 92002-92014,92018-92060,92071,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051, 99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **568**
Condition: UNSPECIFIED URINARY OBSTRUCTION AND BENIGN PROSTATIC HYPERPLASIA WITHOUT OBSTRUCTION (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: N40.0,N40.2-N40.3
CPT: 52450,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404, 99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **569**
Condition: OTHER COMPLICATIONS OF A PROCEDURE (See Guideline Notes 6,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: H18.821-H18.829,T81.81XA-T81.81XD,T81.82XA-T81.82XD,T81.9XXA-T81.9XXD
CPT: 38300-38382,38542-38555,38700-38745,38747,38760,49062,49323,49423,93792,93793,97012,97110-97124, 97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239, 99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513,G0514

Line: **570**
Condition: ANEMIAS DUE TO DISEASE (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: D61.811,D63.0-D63.8,D64.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **571**
Condition: PERSONALITY DISORDERS EXCLUDING BORDERLINE AND SCHIZOTYPAL (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F60.0-F60.2,F60.4-F60.7,F60.81-F60.9,F68.8,F69
CPT: 90846,90849,90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224-99226,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0176,G0177,G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004, H0023,H0032-H0034,H0036-H0039,H0045,H2010,H2014,H2021-H2023,H2027,H2032,H2033,S5151,S9484, T1005

Line: **572**
Condition: ACUTE NON-SUPPURATIVE LABYRINTHITIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: H83.01-H83.09
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **573**
Condition: DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT (See Guideline Notes 64,65)
Treatment: EXCISION OF CYST/RHINECTOMY/PROSTHESIS
ICD-10: J34.2-J34.3,M95.0,Q30.8,S02.2XXA,S02.2XXD-S02.2XXG,S03.1XXA-S03.1XXD
CPT: 20912,21325-21335,30115,30117,30124-30420,30465,30520,30580,30620,30630,31020-31200,61782,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: D7260,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **574**
Condition: STOMATITIS AND OTHER DISEASES OF ORAL SOFT TISSUES (See Guideline Notes 64,65)
Treatment: INCISION AND DRAINAGE, MEDICAL THERAPY
ICD-10: K12.1,K12.30-K12.39,K13.1,K13.22-K13.24,K13.4,K13.6,K13.70-K13.79,K14.0
CPT: 40650,40805,40810-40816,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **575**
Condition: CAVUS DEFORMITY OF FOOT; FLAT FOOT; POLYDACTYLY AND SYNDACTYLY OF TOES (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY, ORTHOTIC
ICD-10: M21.40-M21.42,Q66.50-Q66.52,Q69.2-Q69.9,Q70.20-Q70.9
CPT: 11200,26951,27605,27687,27690,27700-27703,28090,28238,28300,28306,28307,28344,28345,28715,28735,29907,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **576**
Condition: INFECTIOUS MONONUCLEOSIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: B27.00-B27.99
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **577**
Condition: URETHRITIS, NON-SEXUALLY TRANSMITTED (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: N34.2-N34.3,N36.2,N36.8-N36.9,N39.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **578**
Condition: CONGENITAL ANOMALIES OF FEMALE GENITAL ORGANS EXCLUDING VAGINA (See Guideline Notes 64,65)
Treatment: SURGICAL TREATMENT
ICD-10: Q50.01-Q50.6,Q51.0,Q51.10-Q51.4,Q51.6,Q51.810-Q51.818,Q51.9,Q52.4
CPT: 57135,57720,58400,58540,58559-58562,58660-58662,58700-58740,58940,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **579**
Condition: THROMBOTIC DISORDERS
Treatment: MEDICAL THERAPY
ICD-10: D68.51-D68.69
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9345

Line: **580**
Condition: CANDIDIASIS OF MOUTH, SKIN AND NAILS (See Guideline Notes 64,65,113)
Treatment: MEDICAL THERAPY
ICD-10: B37.0,B37.2,B37.83,B37.9,K13.0
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **581**
Condition: BENIGN NEOPLASM OF MALE GENITAL ORGANS: TESTIS, PROSTATE, EPIDIDYMIS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: D29.1,D29.20-D29.32,D29.8-D29.9
CPT: 54231,54512,54522,54900,54901,55200,55600-55680,55801,93792,93793,98966-98969,99051,99060,99070, 99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498, 99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **582**
Condition: ATROPHY OF EDENTULOUS ALVEOLAR RIDGE
Treatment: VESTIBULOPLASTY, GRAFTS, IMPLANTS
ICD-10: K08.20-K08.26
CPT: 21210,21215,21244-21249,40840,40842,40845,93792,93793,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: D7340,D7350,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511, G0513,G0514

Line: **583**
Condition: DISEASE OF NAILS, HAIR AND HAIR FOLLICLES (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: L60.0-L60.9,L62,L63.0-L63.9,L64.0-L64.9,L65.0-L65.9,L66.0,L67.0-L67.9,L68.0-L68.9,L73.1,L73.8-L73.9,Q84.0-Q84.6
CPT: 11000,11001,11720-11765,11900,11901,17380,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **584**
Condition: ACUTE TONSILLITIS OTHER THAN BETA-STREPTOCOCCAL (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: J03.80-J03.91
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **585**
Condition: CORNS AND CALLUSES (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: L84
CPT: 11055-11057,17000-17004,17110,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514,S0390

Line: **586**
Condition: SYNOVITIS AND TENOSYNOVITIS (See Guideline Notes 6,64,65)
Treatment: MEDICAL THERAPY
ICD-10: M65.10,M65.111-M65.19,M65.30,M65.311-M65.9,M67.30,M67.311-M67.39
CPT: 20550-20553,20600-20611,25000,26055,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542, 97760-97763,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **587**
Condition: PROLAPSED URETHRAL MUCOSA (See Guideline Notes 64,65)
Treatment: SURGICAL TREATMENT
ICD-10: N36.2,N36.8
CPT: 51840,51841,52270,52285,53000,53010,53275,57220,57230,57267-57270,77321,93792,93793,98966-98969, 99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **588**
Condition: DENTAL CONDITIONS (E.G., CARIES, FRACTURED TOOTH)
Treatment: ADVANCED RESTORATIVE-ELECTIVE (INLAYS, ONLAYS, GOLD FOIL AND HIGH NOBLE METAL RESTORATIONS)
HCPCS: D2410-D2544,D2720-D2750,D2780-D2794,D2929,D2949,D2952,D2953,D2971,D2981,D2982,D4249,D5213, D5214,D5223,D5224,D5281,D5810,D5811,D5862,D5867,D5875,D6205,D6212,D6214,D6253,D6602-D6607, D6610-D6710,D6780-D6790,D6793-D6920,D6940,D6950,D9950

Line: **589**
Condition: SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS (See Guideline Notes 7,11,12,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: C26.0-C26.9,C45.7-C45.9,C7A.1-C7A.8,C7B.00-C7B.8,C76.1-C76.3,C76.40-C76.8,C77.0-C77.9,C78.00-C78.6, C78.80-C78.89,C79.81-C79.9,C80.0-C80.1,D44.9,Z85.020,Z85.030,Z85.040,Z85.060,Z85.110,Z85.230,Z85.520, Z85.821,Z85.858
CPT: 11600-11646,32553,36260-36262,38720,38724,38745,41110-41114,41130,42120,42842-42845,43195,43196, 43212-43214,43216-43229,43233,43248-43250,43266,43270,47420,47425,47610,47741,47785,49411,58951, 60600-60650,61500,61510,61517-61521,61546,61548,61586,77014,77261-77295,77300-77370,77385-77387, 77401-77432,77469,77470,77761-77763,77770-77790,79005-79445,93792,93793,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285, 99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G6001-G6017,S9537

Line: **590**
Condition: GANGLION (See Guideline Notes 64,65,149)
Treatment: EXCISION
ICD-10: M67.40,M67.411-M67.49,M71.30,M71.311-M71.39
CPT: 10140,10160,20551-20553,20612,25111,25112,26160,28090,49185,93792,93793,98966-98969,99051,99060, 99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **591**
Condition: EPISCLERITIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: H15.101-H15.129
CPT: 92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060, 99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498, 99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **592**
Condition: DIAPER RASH (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: L22
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **593**
Condition: TONGUE TIE AND OTHER ANOMALIES OF TONGUE (See Guideline Note 139)
Treatment: FRENOTOMY, TONGUE TIE
ICD-10: Q38.1-Q38.3
CPT: 40819,41010,41115,92526,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285, 99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **594**
Condition: INCONSEQUENTIAL CYSTS OF ORAL SOFT TISSUES (See Guideline Notes 64,65)
Treatment: INCISION AND DRAINAGE
ICD-10: K06.2,K06.8-K06.9,K09.8-K09.9,K11.1,K13.5
CPT: 40800,41005-41009,41015-41018,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: D7460,D7461,G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **595**
Condition: CONGENITAL DEFORMITIES OF KNEE (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: M67.50-M67.52,Q68.2,Q74.1
CPT: 27403-27416,27420-27429,27435,27465-27468,27656,29871-29889,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **596**
Condition: CHRONIC PANCREATITIS
Treatment: SURGICAL TREATMENT
ICD-10: K86.0-K86.1
CPT: 48020,48120,48548,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **597**
Condition: HERPES SIMPLEX WITHOUT COMPLICATIONS, EXCLUDING GENITAL HERPES (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: B00.1,B00.9,B10.81-B10.89
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **598**
Condition: DENTAL CONDITIONS (E.G., MISSING TEETH)
Treatment: COMPLEX PROSTHODONTICS (I.E., FIXED BRIDGES, OVERDENTURES)
HCPCS: D5863-D5866,D6211,D6241,D6242,D6251,D6252,D6545,D6549,D6751,D6752,D6791,D6792

Line: **599**
Condition: CONGENITAL ANOMALIES OF THE EAR WITHOUT IMPAIRMENT OF HEARING; UNILATERAL ANOMALIES OF THE EAR
Treatment: OTOPLASTY, REPAIR AND AMPUTATION
ICD-10: Q16.2,Q17.0-Q17.9,Z01.12
CPT: 21086,21089,69110,69300,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: D5914,D5927,D5992,D5993,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **600**
Condition: KELOID SCAR; OTHER ABNORMAL GRANULATION TISSUE (See Guideline Note 12)
Treatment: INTRALESIONAL INJECTIONS/DESTRUCTION/EXCISION, RADIATION THERAPY
ICD-10: L91.0,L92.9,Z51.0
CPT: 11200,11201,11400-11446,11900,11901,12032,17000-17004,32553,49411,77014,77261-77295,77300-77307,77331-77338,77385-77387,77401-77427,77469,77470,79005-79445,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514,G6001-G6017

Line: **601**
Condition: DISORDERS OF SOFT TISSUE (See Guideline Notes 64,65,149)
Treatment: MEDICAL THERAPY
ICD-10: M43.6,M60.80,M60.811-M60.9,M70.80,M70.811-M70.99,M72.9,M79.0-M79.2,M79.4,M79.81-M79.9,S13.5XXA-S13.5XXD,S16.8XXA-S16.8XXD,S16.9XXA-S16.9XXD,S19.9XXA-S19.9XXD,T14.8XXA-T14.8XXD,Z45.42
CPT: 11042,11045,20550,49185,93792,93793,95990,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: 602
Condition: MINOR BURNS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: L00,L55.0-L55.1,L55.9,T20.00XA-T20.00XD,T20.011A-T20.011D,T20.012A-T20.012D,T20.019A-T20.019D,T20.02XA-T20.02XD,T20.03XA-T20.03XD,T20.04XA-T20.04XD,T20.05XA-T20.05XD,T20.06XA-T20.06XD,T20.07XA-T20.07XD,T20.09XA-T20.09XD,T20.10XA-T20.10XD,T20.111A-T20.111D,T20.112A-T20.112D,T20.119A-T20.119D,T20.12XA-T20.12XD,T20.13XA-T20.13XD,T20.14XA-T20.14XD,T20.15XA-T20.15XD,T20.16XA-T20.16XD,T20.17XA-T20.17XD,T20.19XA-T20.19XD,T20.20XA-T20.20XD,T20.211A-T20.211D,T20.212A-T20.212D,T20.219A-T20.219D,T20.22XA-T20.22XD,T20.23XA-T20.23XD,T20.24XA-T20.24XD,T20.25XA-T20.25XD,T20.26XA-T20.26XD,T20.27XA-T20.27XD,T20.29XA-T20.29XD,T20.40XA-T20.40XD,T20.411A-T20.411D,T20.412A-T20.412D,T20.419A-T20.419D,T20.42XA-T20.42XD,T20.43XA-T20.43XD,T20.44XA-T20.44XD,T20.45XA-T20.45XD,T20.46XA-T20.46XD,T20.47XA-T20.47XD,T20.49XA-T20.49XD,T20.50XA-T20.50XD,T20.511A-T20.511D,T20.512A-T20.512D,T20.519A-T20.519D,T20.52XA-T20.52XD,T20.53XA-T20.53XD,T20.54XA-T20.54XD,T20.55XA-T20.55XD,T20.56XA-T20.56XD,T20.57XA-T20.57XD,T20.59XA-T20.59XD,T20.60XA-T20.60XD,T20.611A-T20.611D,T20.612A-T20.612D,T20.619A-T20.619D,T20.62XA-T20.62XD,T20.63XA-T20.63XD,T20.64XA-T20.64XD,T20.65XA-T20.65XD,T20.66XA-T20.66XD,T20.67XA-T20.67XD,T20.69XA-T20.69XD,T21.00XA-T21.00XD,T21.01XA-T21.01XD,T21.02XA-T21.02XD,T21.03XA-T21.03XD,T21.04XA-T21.04XD,T21.05XA-T21.05XD,T21.06XA-T21.06XD,T21.07XA-T21.07XD,T21.09XA-T21.09XD,T21.10XA-T21.10XD,T21.11XA-T21.11XD,T21.12XA-T21.12XD,T21.13XA-T21.13XD,T21.14XA-T21.14XD,T21.15XA-T21.15XD,T21.16XA-T21.16XD,T21.17XA-T21.17XD,T21.19XA-T21.19XD,T21.20XA-T21.20XD,T21.21XA-T21.21XD,T21.22XA-T21.22XD,T21.23XA-T21.23XD,T21.24XA-T21.24XD,T21.25XA-T21.25XD,T21.26XA-T21.26XD,T21.27XA-T21.27XD,T21.29XA-T21.29XD,T21.40XA-T21.40XD,T21.41XA-T21.41XD,T21.42XA-T21.42XD,T21.43XA-T21.43XD,T21.44XA-T21.44XD,T21.45XA-T21.45XD,T21.46XA-T21.46XD,T21.47XA-T21.47XD,T21.49XA-T21.49XD,T21.50XA-T21.50XD,T21.51XA-T21.51XD,T21.52XA-T21.52XD,T21.53XA-T21.53XD,T21.54XA-T21.54XD,T21.55XA-T21.55XD,T21.56XA-T21.56XD,T21.57XA-T21.57XD,T21.59XA-T21.59XD,T21.60XA-T21.60XD,T21.61XA-T21.61XD,T21.62XA-T21.62XD,T21.63XA-T21.63XD,T21.64XA-T21.64XD,T21.65XA-T21.65XD,T21.66XA-T21.66XD,T21.67XA-T21.67XD,T21.69XA-T21.69XD,T22.00XA-T22.00XD,T22.011A-T22.011D,T22.012A-T22.012D,T22.019A-T22.019D,T22.021A-T22.021D,T22.022A-T22.022D,T22.029A-T22.029D,T22.031A-T22.031D,T22.032A-T22.032D,T22.039A-T22.039D,T22.041A-T22.041D,T22.042A-T22.042D,T22.049A-T22.049D,T22.051A-T22.051D,T22.052A-T22.052D,T22.059A-T22.059D,T22.061A-T22.061D,T22.062A-T22.062D,T22.069A-T22.069D,T22.091A-T22.091D,T22.092A-T22.092D,T22.099A-T22.099D,T22.10XA-T22.10XD,T22.111A-T22.111D,T22.112A-T22.112D,T22.119A-T22.119D,T22.121A-T22.121D,T22.122A-T22.122D,T22.129A-T22.129D,T22.131A-T22.131D,T22.132A-T22.132D,T22.139A-T22.139D,T22.141A-T22.141D,T22.142A-T22.142D,T22.149A-T22.149D,T22.151A-T22.151D,T22.152A-T22.152D,T22.159A-T22.159D,T22.161A-T22.161D,T22.162A-T22.162D,T22.169A-T22.169D,T22.191A-T22.191D,T22.192A-T22.192D,T22.199A-T22.199D,T22.20XA-T22.20XD,T22.211A-T22.211D,T22.212A-T22.212D,T22.219A-T22.219D,T22.221A-T22.221D,T22.222A-T22.222D,T22.229A-T22.229D,T22.231A-T22.231D,T22.232A-T22.232D,T22.239A-T22.239D,T22.241A-T22.241D,T22.242A-T22.242D,T22.249A-T22.249D,T22.251A-T22.251D,T22.252A-T22.252D,T22.259A-T22.259D,T22.261A-T22.261D,T22.262A-T22.262D,T22.269A-T22.269D,T22.291A-T22.291D,T22.292A-T22.292D,T22.299A-T22.299D,T22.40XA-T22.40XD,T22.411A-T22.411D,T22.412A-T22.412D,T22.419A-T22.419D,T22.421A-T22.421D,T22.422A-T22.422D,T22.429A-T22.429D,T22.431A-T22.431D,T22.432A-T22.432D,T22.439A-T22.439D,T22.441A-T22.441D,T22.442A-T22.442D,T22.449A-T22.449D,T22.451A-T22.451D,T22.452A-T22.452D,T22.459A-T22.459D,T22.461A-T22.461D,T22.462A-T22.462D,T22.469A-T22.469D,T22.491A-T22.491D,T22.492A-T22.492D,T22.499A-T22.499D,T22.50XA-T22.50XD,T22.511A-T22.511D,T22.512A-T22.512D,T22.519A-T22.519D,T22.521A-T22.521D,T22.522A-T22.522D,T22.529A-T22.529D,T22.531A-T22.531D,T22.532A-T22.532D,T22.539A-T22.539D,T22.541A-T22.541D,T22.542A-T22.542D,T22.549A-T22.549D,T22.551A-T22.551D,T22.552A-T22.552D,T22.559A-T22.559D,T22.561A-T22.561D,T22.562A-T22.562D,T22.569A-T22.569D,T22.591A-T22.591D,T22.592A-T22.592D,T22.599A-T22.599D,T22.60XA-T22.60XD,T22.611A-T22.611D,T22.612A-T22.612D,T22.619A-T22.619D,T22.621A-T22.621D,T22.622A-T22.622D,T22.629A-T22.629D,T22.631A-T22.631D,T22.632A-T22.632D,T22.639A-T22.639D,T22.641A-T22.641D,T22.642A-T22.642D,T22.649A-T22.649D,T22.651A-T22.651D,T22.652A-T22.652D,T22.659A-T22.659D,T22.661A-T22.661D,T22.662A-T22.662D,T22.669A-T22.669D,T22.691A-T22.691D,T22.692A-T22.692D,T22.699A-T22.699D,T23.001A-T23.001D,T23.002A-T23.002D,T23.009A-T23.009D,T23.011A-T23.011D,T23.012A-T23.012D,T23.019A-T23.019D,T23.021A-T23.021D,T23.022A-T23.022D,T23.029A-T23.029D,T23.031A-T23.031D,T23.032A-T23.032D,T23.039A-T23.039D,T23.041A-T23.041D,T23.042A-T23.042D,T23.049A-T23.049D,T23.051A-T23.051D,T23.052A-T23.052D,T23.059A-T23.059D,T23.061A-T23.061D,T23.062A-T23.062D,T23.069A-T23.069D,T23.071A-T23.071D,T23.072A-T23.072D,T23.079A-T23.079D,T23.091A-T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CPT: 11000,11001,11042-11047,11960-11971,16000-16030,93792,93793,98966-98969,99051,99060,99070,99078,
99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607

HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: 603
Condition: DISORDERS OF SLEEP WITHOUT SLEEP APNEA (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: F10.182,F10.282,F10.982,F11.182,F11.282,F11.982,F13.182,F13.282,F13.982,F14.182,F14.282,F14.982,
F15.182,F15.282,F15.982,F19.182,F19.282,F19.982,F51.01-F51.9,G25.70-G25.81,G25.89,G26,G47.00-G47.29,
G47.32,G47.50-G47.51,G47.53-G47.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,
99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: 604
Condition: ORAL APHTHAE (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: K12.0
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,
99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **605**
Condition: SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR (See Guideline Notes 6,64,65,97,98)
Treatment: MEDICAL THERAPY
ICD-10: M22.2X1-M22.92,M23.000-M23.92,M24.20,M24.211-M24.28,M24.661-M24.669,Q68.6,S03.8XXA-S03.8XXD,
S03.9XXA-S03.9XXD,S23.41XA-S23.41XD,S23.420A-S23.420D,S23.421A-S23.421D,S23.428A-S23.428D,
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S39.011A-S39.011D,S39.012A-S39.012D,S39.013A-S39.013D,S43.401A-S43.401D,S43.402A-S43.402D,
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CPT: 24341,27347,27590,29240-29280,29520-29550,93792,93793,97012,97110-97124,97140-97168,97530,97535, 97542,97760-97763,98925-98942,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **606**
Condition: ASYMPTOMATIC URTICARIA (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: L50.2-L50.4,L50.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **607**
Condition: FINGERTIP AVULSION
Treatment: REPAIR WITHOUT PEDICLE GRAFT
ICD-10: S61.001A-S61.001D,S61.002A-S61.002D,S61.009A-S61.009D,S61.011A-S61.011D,S61.012A-S61.012D, S61.019A-S61.019D,S61.031A-S61.031D,S61.032A-S61.032D,S61.039A-S61.039D,S61.051A-S61.051D, S61.052A-S61.052D,S61.059A-S61.059D,S61.101A-S61.101D,S61.102A-S61.102D,S61.109A-S61.109D, S61.111A-S61.111D,S61.112A-S61.112D,S61.119A-S61.119D,S61.131A-S61.131D,S61.132A-S61.132D, S61.139A-S61.139D,S61.151A-S61.151D,S61.152A-S61.152D,S61.159A-S61.159D,S61.200A-S61.200D, S61.201A-S61.201D,S61.202A-S61.202D,S61.203A-S61.203D,S61.204A-S61.204D,S61.205A-S61.205D, S61.206A-S61.206D,S61.207A-S61.207D,S61.208A-S61.208D,S61.209A-S61.209D,S61.210A-S61.210D, S61.211A-S61.211D,S61.212A-S61.212D,S61.213A-S61.213D,S61.214A-S61.214D,S61.215A-S61.215D, S61.216A-S61.216D,S61.217A-S61.217D,S61.218A-S61.218D,S61.219A-S61.219D,S61.230A-S61.230D, S61.231A-S61.231D,S61.232A-S61.232D,S61.233A-S61.233D,S61.234A-S61.234D,S61.235A-S61.235D, S61.236A-S61.236D,S61.237A-S61.237D,S61.238A-S61.238D,S61.239A-S61.239D,S61.250A-S61.250D, S61.251A-S61.251D,S61.252A-S61.252D,S61.253A-S61.253D,S61.254A-S61.254D,S61.255A-S61.255D, S61.256A-S61.256D,S61.257A-S61.257D,S61.258A-S61.258D,S61.259A-S61.259D,S61.300A-S61.300D, S61.301A-S61.301D,S61.302A-S61.302D,S61.303A-S61.303D,S61.304A-S61.304D,S61.305A-S61.305D, S61.306A-S61.306D,S61.307A-S61.307D,S61.308A-S61.308D,S61.309A-S61.309D,S61.310A-S61.310D, S61.311A-S61.311D,S61.312A-S61.312D,S61.313A-S61.313D,S61.314A-S61.314D,S61.315A-S61.315D, S61.316A-S61.316D,S61.317A-S61.317D,S61.318A-S61.318D,S61.319A-S61.319D,S61.330A-S61.330D, S61.331A-S61.331D,S61.332A-S61.332D,S61.333A-S61.333D,S61.334A-S61.334D,S61.335A-S61.335D, S61.336A-S61.336D,S61.337A-S61.337D,S61.338A-S61.338D,S61.339A-S61.339D,S61.350A-S61.350D, S61.351A-S61.351D,S61.352A-S61.352D,S61.353A-S61.353D,S61.354A-S61.354D,S61.355A-S61.355D, S61.356A-S61.356D,S61.357A-S61.357D,S61.358A-S61.358D,S61.359A-S61.359D
CPT: 12001,12002,14350,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **608**
Condition: ABUSE OF NONADDICTIVE SUBSTANCES
Treatment: MEDICAL THERAPY
ICD-10: F55.0-F55.8
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99324-99357,99366,99408,99409,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004-H0006,H0015,H0016,H0032-H0035,H0038,H2010,H2013,H2033,H2035,T1006,T1007,T1502

Line: **609**
Condition: MINOR HEAD INJURY: HEMATOMA/EDEMA WITH NO PERSISTENT SYMPTOMS (See Guideline Notes 64,65,121)
Treatment: MEDICAL THERAPY
ICD-10: S02.0XXA,S02.101A,S02.101D-S02.101G,S02.102A,S02.102D-S02.102G,S02.109A,S02.109D-S02.109G,S02.110A,S02.111A,S02.112A,S02.113A,S02.118A,S02.119A,S02.11AA,S02.11AD-S02.11AG,S02.11BA,S02.11BD-S02.11BG,S02.11CA,S02.11CD-S02.11CG,S02.11DA,S02.11DD-S02.11DG,S02.11EA,S02.11ED-S02.11EG,S02.11FA,S02.11FD-S02.11FG,S02.11GA,S02.11GD-S02.11GG,S02.11HA,S02.11HD-S02.11HG,S02.19XA,S02.80XA-S02.80XG,S02.91XA,S06.0X0A-S06.0X0D,S06.2X0A-S06.2X0D,S06.300A-S06.300D,S06.310A-S06.310D,S06.320A-S06.320D,S06.330A-S06.330D,S06.370A-S06.370D
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **610**
Condition: VIRAL WARTS EXCLUDING VENEREAL WARTS (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT, CRYOSURGERY
ICD-10: B07.0-B07.9,B08.1
CPT: 11055-11057,11420-11424,11900,11901,17000-17004,17110,17111,28039-28043,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **611**
Condition: ACUTE UPPER RESPIRATORY INFECTIONS AND COMMON COLD (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: J00,J06.0-J06.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **612**
Condition: OTHER VIRAL INFECTIONS (See Guideline Notes 61,64,65)
Treatment: MEDICAL THERAPY
ICD-10: A88.1,B01.81-B01.9,B03-B04,B05.3-B05.4,B05.81-B05.9,B06.89-B06.9,B08.010-B08.09,B08.20-B08.8,B09,B25.8-B25.9,B26.0-B26.2,B26.81,B26.83-B26.9,B33.0,B33.20-B33.3,B33.8,B34.0-B34.9,B97.0,B97.10-B97.19,B97.29-B97.89
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **613**
Condition: PHARYNGITIS AND LARYNGITIS AND OTHER DISEASES OF VOCAL CORDS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: J02.8-J02.9,J04.0,J04.30,J37.0-J37.1,J38.2
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **614**
Condition: ANOMALIES OF RELATIONSHIP OF JAW TO CRANIAL BASE, MAJOR ANOMALIES OF JAW SIZE, OTHER SPECIFIED AND UNSPECIFIED DENTOFACIAL ANOMALIES (See Guideline Notes 64,65)
Treatment: OSTEOPLASTY, MAXILLA/MANDIBLE
ICD-10: M26.00-M26.20,M26.71-M26.9,M27.0,M27.51-M27.59
CPT: 21120-21127,21145-21160,21193-21209,21255,21295,21296,30520,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: D7940-D7949,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **615**
Condition: DENTAL CONDITIONS (E.G., MALOCCLUSION)
Treatment: ORTHODONTIA (I.E., FIXED AND REMOVABLE APPLIANCES AND ASSOCIATED SURGICAL PROCEDURES)
ICD-10: M26.211-M26.29,M26.31,M26.33-M26.37,M26.4,M26.70,Z46.4
HCPCS: D0340,D0350,D7280-D7283,D7290-D7294,D7296,D7297,D8010-D8694

Line: **616**
Condition: DENTAL CONDITIONS (E.G., MISSING TEETH)
Treatment: IMPLANTS (I.E., IMPLANT PLACEMENT AND ASSOCIATED CROWN OR PROSTHESIS)
ICD-10: M27.61-M27.69
HCPCS: D0393-D0395,D6010-D6095,D6100-D6194,D6210,D6240,D6245,D6250,D7951,D7952

Line: **617**
Condition: BENIGN LESIONS OF TONGUE (See Guideline Notes 64,65)
Treatment: EXCISION
ICD-10: K13.21,K13.3,K14.1-K14.9
CPT: 41110-41114,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **618**
Condition: UNCOMPLICATED HEMORRHOIDS (See Guideline Notes 64,65)
Treatment: HEMORRHOIDECTOMY, MEDICAL THERAPY
ICD-10: K64.0-K64.2,K64.8-K64.9
CPT: 44391,45317,45334,45335,45350,45381,45382,45398,46083,46220-46262,46320,46500,46610-46615,46930,46945-46947,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **619**
Condition: PREVENTION SERVICES WITH LIMITED OR NO EVIDENCE OF EFFECTIVENESS (See Guideline Notes 64,65,106)
Treatment: MEDICAL THERAPY
ICD-10: Q92.61,Q95.0-Q95.1,Q95.9,Z12.12,Z12.39,Z12.5,Z12.81,Z12.83,Z13.6,Z22.0-Z22.2,Z22.31,Z22.321-Z22.322,Z22.338-Z22.9,Z71.3,Z71.42,Z71.52,Z71.82,Z79.810
CPT: 58940,76706,90749,93792,93793,96110,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0117,G0118,G0248-G0250,G0396,G0397,G0446,G0451,G0463-G0467,G0490,G0511,G0513,G0514

Line: **620**
Condition: OPEN WOUND OF INTERNAL STRUCTURES OF MOUTH WITHOUT COMPLICATION (See Guideline Notes 64,65)
Treatment: REPAIR SOFT TISSUES
ICD-10: K08.123,S01.501A-S01.501D,S01.502A-S01.502D,S01.512A-S01.512D,S01.532A-S01.532D,S01.552A-S01.552D
CPT: 12001-12020,12031-12057,13131-13153,40831,41250,41251,42180,42182,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 621
Condition: SEBACEOUS CYST (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: L05.91-L05.92,L72.0,L72.11-L72.9
CPT: 10060,10061,11400-11446,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285, 99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: 622
Condition: SEBORRHEIC KERATOSIS, DYSCHROMIA, AND VASCULAR DISORDERS, SCAR CONDITIONS, AND FIBROSIS OF SKIN (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: E65,L11.1,L44.8-L44.9,L82.0-L82.1,L90.5,L92.1,L94.2,L94.4,L95.0,L95.8-L95.9,L98.8-L98.9,S00.241A-S00.241D, S00.242A-S00.242D,S00.249A-S00.249D
CPT: 11000,11042,11045,11055-11057,11400-11446,13100-13160,15780-15793,15830-15839,15876-15879,17000-17108,17360,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378, 99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: 623
Condition: REDUNDANT PREPUCE (See Guideline Notes 64,65)
Treatment: ELECTIVE CIRCUMCISION
ICD-10: N47.3-N47.4,N47.7-N47.8,Z41.2
CPT: 54000,54001,54150-54164,54450,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: 624
Condition: CONJUNCTIVAL CYST (See Guideline Notes 64,65)
Treatment: EXCISION OF CONJUNCTIVAL CYST
ICD-10: H11.211-H11.229,H11.30-H11.33,H11.411-H11.419,H11.431-H11.449
CPT: 68020,68040,68110,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480, 99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: 625
Condition: BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES (See Guideline Notes 13,64,65)
Treatment: MEDICAL THERAPY
ICD-10: D10.0-D10.2,D10.30-D10.9,D11.0-D11.9,D17.0-D17.1,D17.20-D17.6,D17.72,D17.9,D18.00-D18.01,D18.09-D18.1,D19.7-D19.9,D22.0,D22.10-D22.9,D23.0,D23.10-D23.9,D28.0-D28.9,D29.0,D29.4,D36.0,D36.7-D36.9, D3A.00,D3A.098-D3A.8,L08.9,L57.0,L92.8,L98.0
CPT: 11400-11446,12031,12032,13100-13151,17000-17108,21011-21014,21552,21554,21931-21933,22901-22903, 23071,23073,24071,24073,25071,25073,26111,26113,27043,27045,27337,27339,27632,27634,28039,28041, 37241,37242,40500-40530,40810-40816,40820,41116,41826,42104-42107,42160,42808,69145,93792,93793, 96567,96573,96574,96904,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378, 99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: D7450-D7460,D7981,G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: 626
Condition: DISEASE OF CAPILLARIES
Treatment: EXCISION
ICD-10: I78.1-I78.9,I79.8
CPT: 11400-11426,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378, 99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: 627
Condition: BENIGN CERVICAL CONDITIONS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: N84.1,N84.3,N88.1-N88.2,N88.4-N88.9,N89.8,N90.3,N90.7,N90.89-N90.9
CPT: 56441,56805,57061,57065,57200,57800,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215, 99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **628**
Condition: CYST, HEMORRHAGE, AND INFARCTION OF THYROID (See Guideline Notes 64,65,149)
Treatment: SURGICAL TREATMENT
ICD-10: E04.1,E07.89-E07.9
CPT: 49185,60200-60225,60270,60271,60300,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **629**
Condition: PICA (See Coding Specification Below) (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F50.89,F98.3
CPT: 90785,90832-90840,90847,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514

ICD-10 F50.89 is included on Line 381 for psychogenic loss of appetite. ICD-10 F50.89 is included on Line 629 for pica in adults and for all other diagnoses using this code.

Line: **630**
Condition: ACUTE VIRAL CONJUNCTIVITIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: B30.0-B30.9,H10.30-H10.33
CPT: 92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **631**
Condition: MUSCULAR CALCIFICATION AND OSSIFICATION (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: M61.00,M61.011-M61.9
CPT: 27036,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **632**
Condition: SUPERFICIAL WOUNDS WITHOUT INFECTION AND CONTUSIONS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: S00.00XA-S00.00XD,S00.01XA-S00.01XD,S00.02XA-S00.02XD,S00.03XA-S00.03XD,S00.04XA-S00.04XD,S00.05XA-S00.05XD,S00.06XA-S00.06XD,S00.07XA-S00.07XD,S00.10XA-S00.10XD,S00.11XA-S00.11XD,S00.12XA-S00.12XD,S00.201A-S00.201D,S00.202A-S00.202D,S00.209A-S00.209D,S00.211A-S00.211D,S00.212A-S00.212D,S00.219A-S00.219D,S00.221A-S00.221D,S00.222A-S00.222D,S00.229A-S00.229D,S00.261A-S00.261D,S00.262A-S00.262D,S00.269A-S00.269D,S00.271A-S00.271D,S00.272A-S00.272D,S00.279A-S00.279D,S00.30XA-S00.30XD,S00.31XA-S00.31XD,S00.32XA-S00.32XD,S00.33XA-S00.33XD,S00.34XA-S00.34XD,S00.35XA-S00.35XD,S00.36XA-S00.36XD,S00.37XA-S00.37XD,S00.401A-S00.401D,S00.402A-S00.402D,S00.409A-S00.409D,S00.411A-S00.411D,S00.412A-S00.412D,S00.419A-S00.419D,S00.421A-S00.421D,S00.422A-S00.422D,S00.429A-S00.429D,S00.431A-S00.431D,S00.432A-S00.432D,S00.439A-S00.439D,S00.441A-S00.441D,S00.442A-S00.442D,S00.449A-S00.449D,S00.451A-S00.451D,S00.452A-S00.452D,S00.459A-S00.459D,S00.461A-S00.461D,S00.462A-S00.462D,S00.469A-S00.469D,S00.471A-S00.471D,S00.472A-S00.472D,S00.479A-S00.479D,S00.501A-S00.501D,S00.502A-S00.502D,S00.511A-S00.511D,S00.512A-S00.512D,S00.521A-S00.521D,S00.522A-S00.522D,S00.531A-S00.531D,S00.532A-S00.532D,S00.541A-S00.541D,S00.542A-S00.542D,S00.551A-S00.551D,S00.552A-S00.552D,S00.561A-S00.561D,S00.562A-S00.562D,S00.571A-S00.571D,S00.572A-S00.572D,S00.80XA-S00.80XD,S00.81XA-S00.81XD,S00.82XA-S00.82XD,S00.83XA-S00.83XD,S00.84XA-S00.84XD,S00.85XA-S00.85XD,S00.86XA-S00.86XD,S00.87XA-S00.87XD,S00.90XA-S00.90XD,S00.91XA-S00.91XD,S00.92XA-S00.92XD,S00.93XA-S00.93XD,S00.94XA-S00.94XD,S00.95XA-S00.95XD,S00.96XA-S00.96XD,S00.97XA-S00.97XD,S05.10XA-S05.10XD,S05.11XA-S05.11XD,S05.12XA-S05.12XD,S09.10XA-S09.10XD,S09.11XA-S09.11XD,S09.19XA-S09.19XD,S09.8XXA-S09.8XXD,S09.90XA-S09.90XD,S09.92XA-S09.92XD,S09.93XA-S09.93XD,S10.0XXA-S10.0XXD,S10.10XA-S10.10XD,S10.11XA-S10.11XD,S10.12XA-S10.12XD,S10.14XA-S10.14XD,S10.15XA-S10.15XD,S10.16XA-S10.16XD,S10.17XA-S10.17XD,S10.80XA-S10.80XD,S10.81XA-S10.81XD,S10.82XA-S10.82XD,S10.83XA-S10.83XD,S10.84XA-S10.84XD,S10.85XA-S10.85XD,S10.86XA-S10.86XD,S10.87XA-S10.87XD,S10.90XA-S10.90XD,S10.91XA-S10.91XD,S10.92XA-S10.92XD,S10.93XA-S10.93XD,S10.94XA-S10.94XD,S10.95XA-S10.95XD,S10.96XA-S10.96XD,S10.97XA-S10.97XD,S19.80XA-S19.80XD,S19.81XA-S19.81XD,S19.82XA-S19.82XD,S19.83XA-S19.83XD,S19.84XA-S19.84XD,S19.85XA-S19.85XD,S19.89XA-S19.89XD,S20.00XA-S20.00XD,S20.01XA-S20.01XD,S20.02XA-S20.02XD,S20.101A-S20.101D,S20.102A-S20.102D,S20.109A-S20.109D,S20.111A-S20.111D,S20.112A-S20.112D,S20.119A-S20.119D,S20.121A-S20.121D,S20.122A-S20.122D,S20.129A-S20.129D,S20.141A-S20.141D,S20.142A-S20.142D,S20.149A-S20.149D,S20.151A-S20.151D,S20.152A-S20.152D,S20.159A-S20.159D,S20.161A-S20.161D,

S20.162A-S20.162D,S20.169A-S20.169D,S20.171A-S20.171D,S20.172A-S20.172D,S20.179A-S20.179D,
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S20.222A-S20.222D,S20.229A-S20.229D,S20.301A-S20.301D,S20.302A-S20.302D,S20.309A-S20.309D,
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S70.341A-S70.341D,S70.342A-S70.342D,S70.349A-S70.349D,S70.351A-S70.351D,S70.352A-S70.352D,
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S70.372A-S70.372D,S70.379A-S70.379D,S70.911A-S70.911D,S70.912A-S70.912D,S70.919A-S70.919D,
S70.921A-S70.921D,S70.922A-S70.922D,S70.929A-S70.929D,S76.001A-S76.001D,S76.002A-S76.002D,
S76.009A-S76.009D,S76.091A-S76.091D,S76.092A-S76.092D,S76.099A-S76.099D,S76.101A-S76.101D,
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S76.891A-S76.891D,S76.892A-S76.892D,S76.899A-S76.899D,S76.901A-S76.901D,S76.902A-S76.902D,
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S79.812A-S79.812D,S79.819A-S79.819D,S79.821A-S79.821D,S79.822A-S79.822D,S79.829A-S79.829D, S79.911A-S79.911D,S79.912A-S79.912D,S79.919A-S79.919D,S79.921A-S79.921D,S79.922A-S79.922D, S79.929A-S79.929D,S80.00XA-S80.00XD,S80.01XA-S80.01XD,S80.02XA-S80.02XD,S80.10XA-S80.10XD, S80.11XA-S80.11XD,S80.12XA-S80.12XD,S80.211A-S80.211D,S80.212A-S80.212D,S80.219A-S80.219D, S80.221A-S80.221D,S80.222A-S80.222D,S80.229A-S80.229D,S80.241A-S80.241D,S80.242A-S80.242D, S80.249A-S80.249D,S80.251A-S80.251D,S80.252A-S80.252D,S80.259A-S80.259D,S80.261A-S80.261D, S80.262A-S80.262D,S80.269A-S80.269D,S80.271A-S80.271D,S80.272A-S80.272D,S80.279A-S80.279D, S80.811A-S80.811D,S80.812A-S80.812D,S80.819A-S80.819D,S80.821A-S80.821D,S80.822A-S80.822D, S80.829A-S80.829D,S80.841A-S80.841D,S80.842A-S80.842D,S80.849A-S80.849D,S80.851A-S80.851D, S80.852A-S80.852D,S80.859A-S80.859D,S80.861A-S80.861D,S80.862A-S80.862D,S80.869A-S80.869D, S80.871A-S80.871D,S80.872A-S80.872D,S80.879A-S80.879D,S80.911A-S80.911D,S80.912A-S80.912D, S80.919A-S80.919D,S80.921A-S80.921D,S80.922A-S80.922D,S80.929A-S80.929D,S86.001A-S86.001D, S86.002A-S86.002D,S86.009A-S86.009D,S86.091A-S86.091D,S86.092A-S86.092D,S86.099A-S86.099D, S86.101A-S86.101D,S86.102A-S86.102D,S86.109A-S86.109D,S86.191A-S86.191D,S86.192A-S86.192D, S86.199A-S86.199D,S86.201A-S86.201D,S86.202A-S86.202D,S86.209A-S86.209D,S86.291A-S86.291D, S86.292A-S86.292D,S86.299A-S86.299D,S86.301A-S86.301D,S86.302A-S86.302D,S86.309A-S86.309D, S86.391A-S86.391D,S86.392A-S86.392D,S86.399A-S86.399D,S86.801A-S86.801D,S86.802A-S86.802D, S86.809A-S86.809D,S86.891A-S86.891D,S86.892A-S86.892D,S86.899A-S86.899D,S86.901A-S86.901D, S86.902A-S86.902D,S86.909A-S86.909D,S86.991A-S86.991D,S86.992A-S86.992D,S86.999A-S86.999D, S89.80XA-S89.80XD,S89.81XA-S89.81XD,S89.82XA-S89.82XD,S89.90XA-S89.90XD,S89.91XA-S89.91XD, S89.92XA-S89.92XD,S90.00XA-S90.00XD,S90.01XA-S90.01XD,S90.02XA-S90.02XD,S90.111A-S90.111D, S90.112A-S90.112D,S90.119A-S90.119D,S90.121A-S90.121D,S90.122A-S90.122D,S90.129A-S90.129D, S90.211A-S90.211D,S90.212A-S90.212D,S90.219A-S90.219D,S90.221A-S90.221D,S90.222A-S90.222D, S90.229A-S90.229D,S90.30XA-S90.30XD,S90.31XA-S90.31XD,S90.32XA-S90.32XD,S90.411A-S90.411D, S90.412A-S90.412D,S90.413A-S90.413D,S90.414A-S90.414D,S90.415A-S90.415D,S90.416A-S90.416D, S90.421A-S90.421D,S90.422A-S90.422D,S90.423A-S90.423D,S90.424A-S90.424D,S90.425A-S90.425D, S90.426A-S90.426D,S90.441A-S90.441D,S90.442A-S90.442D,S90.443A-S90.443D,S90.444A-S90.444D, S90.445A-S90.445D,S90.446A-S90.446D,S90.451A-S90.451D,S90.452A-S90.452D,S90.453A-S90.453D, S90.454A-S90.454D,S90.455A-S90.455D,S90.456A-S90.456D,S90.461A-S90.461D,S90.462A-S90.462D, S90.463A-S90.463D,S90.464A-S90.464D,S90.465A-S90.465D,S90.466A-S90.466D,S90.471A-S90.471D, S90.472A-S90.472D,S90.473A-S90.473D,S90.474A-S90.474D,S90.475A-S90.475D,S90.476A-S90.476D, S90.511A-S90.511D,S90.512A-S90.512D,S90.519A-S90.519D,S90.521A-S90.521D,S90.522A-S90.522D, S90.529A-S90.529D,S90.541A-S90.541D,S90.542A-S90.542D,S90.549A-S90.549D,S90.551A-S90.551D, S90.552A-S90.552D,S90.559A-S90.559D,S90.561A-S90.561D,S90.562A-S90.562D,S90.569A-S90.569D, S90.571A-S90.571D,S90.572A-S90.572D,S90.579A-S90.579D,S90.811A-S90.811D,S90.812A-S90.812D, S90.819A-S90.819D,S90.821A-S90.821D,S90.822A-S90.822D,S90.829A-S90.829D,S90.841A-S90.841D, S90.842A-S90.842D,S90.849A-S90.849D,S90.851A-S90.851D,S90.852A-S90.852D,S90.859A-S90.859D, S90.861A-S90.861D,S90.862A-S90.862D,S90.869A-S90.869D,S90.871A-S90.871D,S90.872A-S90.872D, S90.879A-S90.879D,S90.911A-S90.911D,S90.912A-S90.912D,S90.919A-S90.919D,S90.921A-S90.921D, S90.922A-S90.922D,S90.929A-S90.929D,S90.931A-S90.931D,S90.932A-S90.932D,S90.933A-S90.933D, S90.934A-S90.934D,S90.935A-S90.935D,S90.936A-S90.936D,S96.001A-S96.001D,S96.002A-S96.002D, S96.009A-S96.009D,S96.091A-S96.091D,S96.092A-S96.092D,S96.099A-S96.099D,S96.101A-S96.101D, S96.102A-S96.102D,S96.109A-S96.109D,S96.191A-S96.191D,S96.192A-S96.192D,S96.199A-S96.199D, S96.201A-S96.201D,S96.202A-S96.202D,S96.209A-S96.209D,S96.291A-S96.291D,S96.292A-S96.292D, S96.299A-S96.299D,S96.801A-S96.801D,S96.802A-S96.802D,S96.809A-S96.809D,S96.891A-S96.891D, S96.892A-S96.892D,S96.899A-S96.899D,S96.901A-S96.901D,S96.902A-S96.902D,S96.909A-S96.909D, S96.991A-S96.991D,S96.992A-S96.992D,S96.999A-S96.999D,S99.811A-S99.811D,S99.812A-S99.812D, S99.819A-S99.819D,S99.821A-S99.821D,S99.822A-S99.822D,S99.829A-S99.829D,S99.911A-S99.911D, S99.912A-S99.912D,S99.919A-S99.919D,S99.921A-S99.921D,S99.922A-S99.922D,S99.929A-S99.929D, T07.XXXA-T07.XXXD

CPT: 10120,10140,11740,11760,11762,12001-12014,28190,93792,93793,98966-98969,99051,99060,99070,99078, 99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607

HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **633**
Condition: CHRONIC BRONCHITIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: J40,J41.0,J41.8,J42
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **634**
Condition: GALACTORRHEA, MASTODYNIA, ATROPHY, BENIGN NEOPLASMS AND UNSPECIFIED DISORDERS OF THE BREAST (See Guideline Notes 64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: D24.1-D24.9,N64.1-N64.4,N64.81-N64.82,N64.9,Q83.0-Q83.9
CPT: 19110,19120-19126,19324-19396,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239, 99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **635**
Condition: BENIGN POLYPS OF VOCAL CORDS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY, STRIPPING
ICD-10: J38.1
CPT: 31540,31541,31572,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **636**
Condition: BENIGN NEOPLASMS OF DIGESTIVE SYSTEM (See Guideline Notes 64,65)
Treatment: SURGICAL TREATMENT
ICD-10: D13.0-D13.2,D13.30-D13.6,D13.9,D17.79,D18.03,D19.1,D20.0-D20.1,D3A.010-D3A.019,D3A.092,D3A.094-D3A.096,K31.7
CPT: 43195,43196,43212-43214,43216-43229,43233,43245,43248-43250,43266,43270,43450,44110-44120,44139-44145,44204-44208,44213,44369,44379,44381,44384,44392-44402,44404,44405,44701,45160,45308,45309,45317-45327,45333-45335,45338,45346,45347,45381-45389,46610,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **637**
Condition: VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR OTHER MAJOR COMPLICATION (See Guideline Notes 64,65)
Treatment: STRIPPING/SCLEROTHERAPY, MEDICAL THERAPY
ICD-10: I83.811-I83.93,I87.001-I87.009,I87.091-I87.309,I87.391-I87.9,I99.8-I99.9,N48.81,N50.1,R58
CPT: 29584,36465-36479,37700-37790,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **638**
Condition: HYPERTELORISM OF ORBIT (See Guideline Notes 64,65)
Treatment: ORBITOTOMY
ICD-10: H05.89
CPT: 67405,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **639**
Condition: GALLSTONES WITHOUT CHOLECYSTITIS (See Coding Specification Below) (See Guideline Notes 64,65,167)
Treatment: MEDICAL THERAPY, CHOLECYSTECTOMY
ICD-10: K80.20,K80.50,K80.70,K80.80,K82.4-K82.9,K91.5
CPT: 43260-43265,43273-43278,47490,47542,47564,47570,47600-47620,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

ICD-10 K82.8 (Other specified diseases of gallbladder) is included on Line 55 when the patient has porcelain gallbladder or gallbladder dyskinesia with a gallbladder ejection fraction <35%. Otherwise, K82.8 is included on Line 639.

Line: **640**
Condition: GYNECOMASTIA
Treatment: MASTECTOMY
ICD-10: N62
CPT: 19300,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **641**
Condition: TMJ DISORDERS (See Guideline Notes 64,65)
Treatment: TMJ SURGERY
ICD-10: M26.50-M26.59,M26.601-M26.69
CPT: 20910,21010,21050-21073,21210-21243,21480-21490,29800,29804,30520,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: D7852-D7877,D7899,D7955,D7991,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **642**
Condition: EDEMA AND OTHER CONDITIONS INVOLVING THE SKIN OF THE FETUS AND NEWBORN (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: P83.1,P83.30-P83.4,P83.6,P83.81-P83.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **643**
Condition: DENTAL CONDITIONS WHERE TREATMENT IS CHOSEN PRIMARILY FOR AESTHETIC CONSIDERATIONS (See Guideline Notes 64,65)
Treatment: COSMETIC DENTAL SERVICES
ICD-10: K00.1-K00.3,K00.5,K00.8-K00.9,K03.0-K03.1,K03.3-K03.4,K03.6-K03.7,K03.9,M26.30,M26.39
HCPCS: D2610-D2664,D2934,D2960-D2962,D2983,D3460,D4230,D4231,D6548,D6600,D6601,D6608,D6609,D6720-D6750,D6985,D7995,D7996,D9970-D9975

Line: **644**
Condition: DENTAL CONDITIONS WHERE TREATMENT RESULTS IN MARGINAL IMPROVEMENT (See Guideline Notes 64,65)
Treatment: ELECTIVE DENTAL SERVICES
ICD-10: K00.7,K08.0,K08.51-K08.52,K08.54,K08.81-K08.89,M26.32,M85.2
CPT: 41822
HCPCS: D2799,D2955,D2990,D3355-D3357,D3427-D3429,D3431,D3432,D3470,D3920,D3950,D4263,D4264,D5225,D5226,D5994,D7272,D7950,D7953,D7972,D7998,D9910,D9911,D9940-D9943,D9952

Line: **645**
Condition: AGENESIS OF LUNG (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-10: Q33.3
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **646**
Condition: CENTRAL RETINAL ARTERY OCCLUSION
Treatment: PARACENTESIS OF AQUEOUS
ICD-10: H34.10-H34.13,H34.211-H34.239
CPT: 67015,67500,67505,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Line: **647**
Condition: MENTAL DISORDERS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65)
Treatment: EVALUATION
ICD-10: F11.90,F12.90,F13.90,F14.90,F15.90,F16.90,F18.90,F19.90,F48.8,F93.8
CPT: 93792,93793,98966-98969,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514

Line: **648**
Condition: INTRACRANIAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65)
Treatment: EVALUATION
ICD-10: G45.4,G46.3-G46.8,H46.00-H46.9,H47.11-H47.12,H47.311-H47.49,H47.611-H47.649,I68.0,I68.8
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **649**
Condition: INFECTIOUS DISEASES WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65)
Treatment: EVALUATION
ICD-10: A02.29,A80.0-A80.2,A80.30-A80.9,A82.0-A82.9,A85.2,B64,B89,B99.9,L94.6,M60.009
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **650**
Condition: ENDOCRINE AND METABOLIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65)
Treatment: EVALUATION
ICD-10: E01.0-E01.2,E04.0,E04.2-E04.9,E16.0-E16.2,E23.7,E30.9,E32.0,E32.8-E32.9,E34.1,E34.3,E34.8-E34.9,E35, E67.1,E70.40-E70.49,E71.30,E73.1-E73.9,E74.11,E74.9,E75.10,E75.21-E75.22,E75.240-E75.249,E75.3,E75.5, E76.01-E76.1,E76.210-E76.9,E77.0,E77.8-E77.9,E78.71-E78.79,E80.4,E80.6-E80.7,E85.0,E88.89,Q89.1
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **651**
Condition: CARDIOVASCULAR CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65,81)
Treatment: EVALUATION
ICD-10: I51.7,I51.89,I52,I73.1,Q24.0-Q24.1,Q25.47,Q28.9,Q34.1,Q55.5,Q89.3
CPT: 33620,33621,75557,75565,75573,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **652**
Condition: SENSORY ORGAN CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65,131,171)
Treatment: EVALUATION
ICD-10: H02.711-H02.719,H02.731-H02.739,H02.841-H02.859,H02.89-H02.9,H05.00,H05.20,H05.821-H05.9,H11.001-H11.019,H11.031-H11.10,H11.131-H11.139,H11.151-H11.159,H11.811-H11.9,H17.811-H17.89,H18.20,H18.211-H18.219,H18.231-H18.339,H18.411-H18.419,H18.461-H18.469,H18.811-H18.819,H18.891-H18.9,H21.211-H21.309,H21.9,H22,H31.001-H31.099,H31.321-H31.329,H33.111-H33.119,H33.301-H33.309,H33.321-H33.329, H34.821-H34.829,H35.40,H35.411-H35.469,H35.721-H35.739,H35.82-H35.9,H36,H43.391-H43.399,H43.89-H43.9,H44.40,H44.411-H44.419,H44.431-H44.449,H47.011-H47.099,H47.13,H47.20,H47.211-H47.299,H47.511-H47.539,H53.53-H53.55,H53.71-H53.72,H54.40,H54.413A-H54.62,H55.02,H55.04,H55.81-H55.89,H57.00-H57.04,H57.051-H57.09,H57.8-H57.9,H59.40-H59.43,H61.90-H61.93,H62.8X1-H62.8X9,H69.80-H69.83,H75.80-H75.83,H93.11-H93.19
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **653**
Condition: NEUROLOGIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65)
Treatment: EVALUATION
ICD-10: F07.9,F48.2,G24.4,G25.82-G25.89,G31.84,G60.9,G61.9,G62.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **654**
Condition: DERMATOLOGICAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 21,64,65)
Treatment: EVALUATION
ICD-10: B36.0,D69.2,D69.8-D69.9,E88.1,H02.60-H02.66,I73.81,L30.5,L42,L44.0,L44.4,L45,L57.3,L80,L81.0-L81.9,L85.3, L98.7,Q82.1-Q82.2,Q82.4-Q82.5,Q82.8-Q82.9,Q84.8-Q84.9
CPT: 29581,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0429,G0463-G0467,G0490,G0511,G0513,G0514

Line: **655**
Condition: RESPIRATORY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65,105)
Treatment: EVALUATION
ICD-10: J22,J98.3,J98.51-J98.9,J99,P24.10,P24.20,P24.30,Q33.1,Q33.5,Q33.8-Q33.9,Q34.0,Q34.8-Q34.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **656**
Condition: GENITOURINARY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65,72,73)
Treatment: EVALUATION
ICD-10: D30.8-D30.9,E28.0,K64.4,N28.81,N28.83,N28.89,N32.89-N32.9,N33,N37,N39.8,N42.30-N42.39,N44.1-N44.8, N48.6,N48.82-N48.9,N50.89-N50.9,N51,N83.321-N83.329,N83.6,N83.9,N85.4,N85.6,N85.8-N85.9,N90.60-N90.69,N90.810-N90.818,N91.4-N91.5,N93.9,N94.9,N96,N99.83,Q52.120,Q54.0,Q54.4,Q54.9,Q55.0-Q55.1, Q55.20-Q55.22,Q55.29,Q55.61-Q55.9,Q60.3,Q62.4-Q62.5,Q62.60-Q62.62,Q63.0-Q63.9,Q64.11,Q64.70,Q64.72, Q64.75,Q64.8-Q64.9,R39.81,R80.2
CPT: 51860,51865,53080,53085,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285, 99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **657**
Condition: MUSCULOSKELETAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65)
Treatment: EVALUATION
ICD-10: E08.618,E09.618,E10.618,E11.618,E13.618,E78.81-E78.89,E88.2,M06.30,M07.60,M07.611-M07.69,M11.10, M11.111-M11.19,M11.9,M12.30,M12.311-M12.39,M12.80,M12.811-M12.9,M13.0,M13.10,M13.111-M13.179, M21.10,M21.179,M24.00,M24.10,M24.30,M24.40,M24.60,M24.80,M24.9,M25.20,M25.30,M35.5,M35.7,M62.00, M62.011-M62.08,M62.81,M62.831-M62.84,M62.9,M63.80,M63.811-M63.89,M84.38XD-M84.38XG,M84.811-M84.88,M85.10,M85.111-M85.19,M85.80,M85.811-M85.89,M89.30,M89.311-M89.59,M89.8X0-M89.8X9,M95.3-M95.4,M95.9,M96.0,M99.88,M99.9,Q76.5,Q77.2,Q79.9,R29.4
CPT: 93792,93793,97010,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **658**
Condition: GASTROINTESTINAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65)
Treatment: EVALUATION
ICD-10: A04.9,K11.0,K22.4,K22.9,K62.81,K62.89-K62.9,K63.89-K63.9,K75.9,K76.9,K83.5-K83.9,K86.9,K90.41,K92.9, P78.9
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404, 99408-99449,99487-99490,99495-99498,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Line: **659**
Condition: MISCELLANEOUS CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65)
Treatment: EVALUATION
ICD-10: E66.3,E67.2,E67.8,Q18.3-Q18.9,Q30.1-Q30.9,Q67.0-Q67.4,Q67.7-Q67.8,T73.3XXA-T73.3XXD
CPT: 40806,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487,99489,99495,99496,99605-99607
HCPCS: G0248-G0250,G0396,G0397,G0463,G0490,G0511,G0513,G0514

Line: **660**
Condition: CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS (See Guideline Notes 64,65,67,173)
Treatment: SPECIFIED INTERVENTIONS

STATEMENTS OF INTENT

STATEMENT OF INTENT 1: PALLIATIVE CARE

It is the intent of the Commission that palliative care services are covered for patients with a life-threatening or serious progressive illness to alleviate symptoms and improve quality of life.

Palliative care services should include culturally appropriate discussions and medical decision making aligned with patient's personal goals of therapy, assessment of symptom burden, assistance with advance care planning, care coordination, emotional, psychosocial and spiritual support for patients and their families. Palliative care services may be provided concurrently with life prolonging/curative treatments.

Some examples of services associated with an encounter for palliative care (ICD-10 Z51.5) that should be available to patients without regard to Prioritized List line placement:

- A) Inpatient palliative care consultations
  - 1) Hospital Care E&M (CPT 99218-99233)
- B) Outpatient palliative care consultations provided in either the office or home setting
  - 1) E&M Services (CPT 99201-99215)
  - 2) Transitional Care Management Services (CPT 99495-6)
  - 3) Advance Care Planning (CPT 99497-8)
  - 4) Chronic Care Management (CPT 99487-99490)
- C) Psychological support and grief counseling (CPT 99201-99215)
- D) Medical equipment and supplies for the management of symptomatic complications or support activities of daily living
- E) Medications or acupuncture to reduce pain and symptom burden
- F) Surgical procedures or therapeutic interventions to relieve pain or symptom burden

Other services associated with palliative care includes:

- A) Social Work
- B) Clinical Chaplain/ Spiritual Care
- C) Care Coordination

It is NOT the intent of the Commission that coverage for palliative care encompasses those treatments that seek to prolong life despite substantial burdens of treatment and limited chance of benefit. See Guideline Note 12 TREATMENT OF CANCER WITH LITTLE OR NO BENEFIT.

STATEMENT OF INTENT 2: DEATH WITH DIGNITY ACT

It is the intent of the Commission that services under ORS 127.800-127.897 (Oregon Death with Dignity Act) be covered for those that wish to avail themselves to those services. Such services include but are not limited to attending physician visits, consulting physician confirmation, mental health evaluation and counseling, and prescription medications.

STATEMENT OF INTENT 3: LOWER PRIORITY SERVICES

It is the intent of the Commission that therapies that exhibit one or more of the following characteristics generally be given low priority on the Prioritized List:

- A) Marginal or clinically unimportant benefit
- B) Unproven/no benefit
- C) Harms outweigh benefits
- D) very high cost in which the cost does not justify the benefit
- E) significantly greater cost compared to alternate therapies when both have similar benefit
- F) Significant budget impact that could affect the overall Prioritized List funding level

Where possible, the Commission prioritizes pairings of condition and treatment codes to reflect this lower priority, or simply does not pair a procedure code with one or more conditions if it exhibits one of these characteristics. This is, however, impractical in several circumstances:

- A) For diagnostic services appropriate for billing with a variety of diagnoses, including diagnoses representing signs and symptoms as well as diagnoses which otherwise appear above the funding line
- B) For ancillary services such as prescription drugs, supplies, physician-administered drugs or durable medical equipment and not identified by a CPT or HCPCS code appropriate for placement on the Prioritized List
- C) For procedure codes not appropriate for placement in the funded region of the list but which may be billed with many possible diagnoses, some of which are above the funding line while others may be below the funding line

In these circumstances, the HERC identifies the services in Guideline Notes 172 and 173, which are attached to Line 500 or Line 660 in order to make its intent transparent.

STATEMENT OF INTENT 4: ROLE OF THE PRIORITIZED LIST IN COVERAGE

The Commission makes its prioritization decisions based on the best available published evidence about treatments for each condition. The Prioritized List prioritizes health services according to their importance for the population served and the legislature determines where to place the funding line on the Prioritized List.

The Commission recognizes that a condition and treatment pairing above the funding line does not necessarily mean that the service will be covered by the Oregon Health Plan (OHP). There may be other restrictions that apply, such as the service not being medically necessary or appropriate for an individual member. Likewise, the absence of a treatment and condition pairing above the

STATEMENT OF INTENT 4: ROLE OF THE PRIORITIZED LIST IN COVERAGE (CONT'D)

funding line is not meant to be an absolute exclusion from coverage. Coverage may still be authorized under applicable federal and state laws, and Oregon's Medicaid State Plan and Waiver for an individual member. For example, OAR 410-141-0480 (Oregon Health Plan Benefit Package of Covered Services) includes services such as, but not limited to, the following:

- Diagnostic services, subject to the List's diagnostic guideline notes when applicable;
- Ancillary services (such as hospitalization, durable medical equipment, certain medications and anesthesia) provided for conditions appearing above the funding line, subject to the List's ancillary guideline notes when applicable; and
- Services paired with an unfunded condition which is causing or exacerbating a funded condition, the treatments for the funded condition are not working or contraindicated, and treatment of the unfunded condition would improve the outcome of treating the funded condition (the "Comorbidity Rule" OAR 410-141-0480(8)(a through b))

In addition, Oregon's 1115(a) Waiver includes coverage for services such as, but not limited to:

- Services on unfunded lines for children ages from birth through 1
- Services provided for a condition appearing in the funded region of the List in conjunction with federal requirements for Early and Periodic Screening, Diagnosis and Treatment (EPSDT) and Oregon's waiver

As a result, the Prioritized List must be used in conjunction with applicable OHP provisions found in federal and state laws, the State Plan and Waiver in coverage determination.

PRACTICE GUIDELINES

GUIDELINE NOTES FOR ANCILLARY AND DIAGNOSTIC SERVICES
NOT APPEARING ON THE JANUARY 1, 2018 PRIORITIZED LIST
OF HEALTH SERVICES

GUIDELINE NOTES FOR HEALTH SERVICES
THAT APPEAR ON THE JANUARY 1, 2018 PRIORITIZED LIST
OF HEALTH SERVICES

ANCILLARY GUIDELINE A1, NERVE BLOCKS

The Health Evidence Review Commission intends that single injection and continuous nerve blocks (CPT 64400-64450, 64461-64463, 64505-64530) should be covered services if they are required for successful completion of perioperative pain control for, or post-operative recovery from a covered operative procedure when the diagnosis requiring the operative procedure is also covered. Additionally, nerve blocks, are covered services for patients hospitalized with trauma, cancer, or intractable pain conditions, if the underlying condition is a covered diagnosis.

ANCILLARY GUIDELINE A2, SELF-MONITORING OF BLOOD GLUCOSE IN DIABETES

For patients with type 1 diabetes and those with type 2 diabetes using multiple daily insulin injections, home blood glucose monitors and related diabetic supplies are covered.

For patients with type 2 diabetes not requiring multiple daily insulin injections, 50 test strips and related supplies are covered at the time of diagnosis. For those who require diabetic medication that may result in hypoglycemia, up to 50 test strips per 90 days are covered. If there is an acute change in glycemic control or active diabetic medication adjustment, an additional 50 strips are covered.

All diabetic patients who are prescribed diabetic test strips should have a structured education and feedback program for self-monitoring of blood glucose.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

ANCILLARY GUIDELINE A3, IVC FILTERS FOR TRAUMA

It is the intent of the Commission that inferior vena cava (IVC) filter placement (CPT 37191) and subsequent repositioning and removal (CPT 37192, 37193) are covered when medically indicated for hospitalized patients with severe trauma resulting in prolonged hospitalization.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

ANCILLARY GUIDELINE A4, SMOKING CESSATION AND ELECTIVE SURGICAL PROCEDURES

Smoking cessation is required prior to elective surgical procedures for active tobacco users. Cessation is required for at least 4 weeks prior to the procedure and requires objective evidence of abstinence from smoking prior to the procedure.

Elective surgical procedures in this guideline are defined as surgical procedures which are flexible in their scheduling because they do not pose an imminent threat nor require immediate attention within 1 month. Reproductive (i.e. for contraceptive purposes), cancer-related and diagnostic procedures are excluded from this guideline.

The well-studied tests for confirmation of smoking cessation include cotinine levels and exhaled carbon monoxide testing. However, cotinine levels may be positive in nicotine replacement therapy (NRT) users, smokeless tobacco and e-cigarette users (which are not contraindications to elective surgery coverage). In patients using nicotine products aside from combustible cigarettes the following alternatives to urine cotinine to demonstrate smoking cessation may be considered:

- Exhaled carbon monoxide testing
- Anabasine or anatabine testing (NRT or vaping)

Certain procedures, such as lung volume reduction surgery, bariatric surgery, erectile dysfunction surgery, and spinal fusion have 6 month tobacco abstinence requirements. See Guideline Notes 8, 100, 112 and 159.

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

A) Genetic tests are covered as diagnostic, unless they are listed below in section F1 as excluded or have other restrictions listed in this guideline. To be covered, initial screening (e.g. physical exam, medical history, family history, laboratory studies, imaging studies) must indicate that the chance of genetic abnormality is > 10% and results would do at least one of the following:
   1) Change treatment,
   2) Change health monitoring,
   3) Provide prognosis, or
   4) Provide information needed for genetic counseling for patient; or patient's parents, siblings, or children
B) Pretest and posttest genetic counseling is required for presymptomatic and predisposition genetic testing. Pretest and posttest genetic evaluation (which includes genetic counseling) is covered when provided by a suitable trained health professional with expertise and experience in genetics.
   1) "Suitably trained" is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.
C) A more expensive genetic test (generally one with a wider scope or more detailed testing) is not covered if a cheaper (smaller scope) test is available and has, in this clinical context, a substantially similar sensitivity. For example, do not cover CFTR gene sequencing as the first test in a person of Northern European Caucasian ancestry because the gene panels are less expensive and provide substantially similar sensitivity in that context.

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE (CONT'D)

D) Related to genetic testing for patients with breast/ovarian and colon/endometrial cancer or other related cancers suspected to be hereditary, or patients at increased risk to due to family history.
   1) Services are provided according to the Comprehensive Cancer Network Guidelines.
      a) Lynch syndrome (hereditary colorectal, endometrial and other cancers associated with Lynch syndrome) services (CPT 81288, 81292-81300, 81317-81319, 81435, 81436) and familial adenomatous polyposis (FAP) services (CPT 81201-81203) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Colorectal V3.2017 (10/10/17). www.nccn.org.
      b) Breast and ovarian cancer syndrome genetic testing services (CPT 81162, 81211-81217) for women without a personal history of breast, ovarian and other associated cancers should be provided to high risk women as defined by the US Preventive Services Task Force or according to the NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and ovarian. V1.2018 (10/3/17). www.nccn.org.
      c) Breast and ovarian cancer syndrome genetic testing services (CPT 81162, 81211-81217) for women with a personal history of breast, ovarian, and other associated cancers and for men with breast cancer should be provided according to the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian. V1.2018 (10/3/17). www.nccn.org.
      d) PTEN (Cowden syndrome) services (CPT 81321-81323) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Colorectal Screening. V3.2017 (10/10/17). www.nccn.org.
   2) Genetic counseling should precede genetic testing for hereditary cancer whenever possible.
      a) Pre and post-test genetic counseling should be covered when provided by a suitable trained health professional with expertise and experience in cancer genetics. Genetic counseling is recommended for cancer survivors when test results would affect cancer screening.
         i) "Suitably trained" is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.
      b) If timely pre-test genetic counseling is not possible for time-sensitive cases, appropriate genetic testing accompanied by pre- and post- test informed consent and post-test disclosure performed by a board-certified physician with experience in cancer genetics should be covered.
         i) Post-test genetic counseling should be performed as soon as is practical.
   3) If the mutation in the family is known, only the test for that mutation is covered. For example, if a mutation for BRCA 1 has been identified in a family, a single site mutation analysis for that mutation is covered (CPT 81215), while a full sequence BRCA 1 and 2 (CPT 81211) analyses is not. There is one exception, for individuals of Ashkenazi Jewish ancestry with a known mutation in the family, the panel for Ashkenazi Jewish BRCA mutations is covered (CPT 81212).
   4) Costs for rush genetic testing for hereditary breast/ovarian and colon/endometrial cancer is not covered.
   5) Hereditary breast cancer-related disorders genomic sequence analysis panels (CPT 81432, 81433, 81479) are only included if the panel test
      a) Includes at least 5 genes that the NCCN Clinical Practice Guidelines in Oncology - Genetic/Familial High-Risk Assessment: Colorectal V3.2017 (10/10/17) and/or NCCN Clinical Practice Guidelines in Oncology - Genetic/Familial High-Risk Assessment: Breast and Ovarian V1.2018 (10/3/17) include(s) with specific guidance on clinical management; and,
      b) Includes no more than a reasonable number of genes (e.g. 40 genes total).

E) Related to diagnostic evaluation of individuals with intellectual disability (defined as a full scale or verbal IQ < 70 in an individual > age 5), developmental delay (defined as a cognitive index <70 on a standardized test appropriate for children < 5 years of age), Autism Spectrum Disorder, or multiple congenital anomalies:
   1) CPT 81228, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder.
   2) CPT 81229, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities; plus cytogenetic constitutional microarray analysis for single nucleotide polymorphism (SNP) variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder; only if (a) consanguinity and recessive disease is suspected, or (b) uniparental disomy is suspected, or (c) another mechanism is suspected that is not detected by the copy number variant test alone.
   3) CPT 81243, 81244, Fragile X genetic testing is covered for individuals with intellectual disability/developmental delay. Although the yield of Fragile X is 3.5-10%, this is included because of additional reproductive implications.
   4) A visit with the appropriate specialist (often genetics, developmental pediatrics, or child neurology), including physical exam, medical history, and family history is covered. Physical exam, medical history, and family history by the appropriate specialist, prior to any genetic testing is often the most cost-effective strategy and is encouraged.

F) Related to other tests with specific CPT codes:
   1) Certain genetic tests have not been found to have proven clinical benefit. These tests are listed in Guideline Note 173, INTERVENTIONS THAT HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS; UNPROVEN INTERVENTIONS
   2) The following tests are covered only if they meet the criteria in section A above AND the specified situations:
      a) CPT 81205, BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X): Cover only when the newborn screening test is abnormal and serum amino acids are normal
      b) Diagnostic testing for cystic fibrosis (CF)

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE (CONT'D)

i) CFTR, cystic fibrosis transmembrane conductance regulator tests. CPT 81220, 81222, 81223: For infants with a positive newborn screen for cystic fibrosis or who are symptomatic for cystic fibrosis, or for clients that have previously been diagnosed with cystic fibrosis but have not had genetic testing, CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered. If two mutations are not identified, CFTR full gene sequencing (CPT 81223) is covered. If two mutations are still not identified, duplication/deletion testing (CPT 81222) is covered. These tests may be ordered as reflex testing on the same specimen.

c) Carrier testing for cystic fibrosis
   i) CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered once in a lifetime.

d) CPT 81224, CFTR (cystic fibrosis transmembrane conductance regulator) (eg. cystic fibrosis) gene analysis; introm 8 poly-T analysis (eg. male infertility): Covered only after genetic counseling.

e) CPT 81240. F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant: Factor 2 20210G>A testing should not be covered for adults with idiopathic venous thromoboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.

f) CPT 81241. F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant: Factor V Leiden testing should not be covered for: adults with idiopathic venous thromoboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.

g) CPT 81247. G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-) should only be covered
   i) After G6PD enzyme activity testing is done and found to be normal; AND either
      (a) There is an urgent clinical reason to know if a deficiency is present, e.g. in a case of acute hemolysis; OR
      (b) In situations where the enzyme activity could be unreliable, e.g. female carrier with extreme Lyonization.

h) CPT 81248. G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; known familial variant(s) is only covered when the information is required for genetic counseling.

i) CPT 81249. G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; full gene sequence is only covered
   i) after G6PD enzyme activity has been tested, and
   ii) the requirements under CPT 81247 above have been met, and
   iii) common variants (CPT 81247) have been tested for and not found.

j) CPT 81256, HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D): Covered for diagnostic testing of patients with elevated transferrin saturation or ferritin levels. Covered for predictive testing ONLY when a first degree family member has treatable iron overload from HFE.

k) CPT 81221, SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z): The alpha-1-antitrypsin protein level should be the first line test for a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle age individual with unexplained dyspnea. Genetic testing of the anpha-1 phenotype test is appropriate if the protein test is abnormal or borderline. The genetic test is appropriate for siblings of people with AAT deficiency regardless of the AAT protein test results.

l) CPT 81415-81416, exome testing: A genetic counseling/geneticist consultation is required prior to ordering test

m) CPT 81430-81431, Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel: Testing for mutations in GJB2 and GJB6 need to be done first and be negative in non-syndromic patients prior to panel testing.

n) CPT 81440, 81460, 81465, mitochondrial genome testing: A genetic counseling/geneticist or metabolic consultation is required prior to ordering test.

o) CPT 81412 Ashkenazi Jewish carrier testing panel: panel testing is only covered when the panel would replace and would be similar or lower cost than individual gene testing including CF carrier testing.

* American College of Medical Genetics Standards and Guidelines for Clinical Genetics Laboratories. 2008 Edition, Revised 3/2011 and found at https://www.acmg.net/StaticContent/SGs/CFTR%20Mutation%20Testing.pdf.

DIAGNOSTIC GUIDELINE D2, IMPLANTABLE CARDIAC LOOP RECORDERS

Use of an implantable cardiac loop recorder (ICLR) is a covered service only when the patient meets all of the following criteria:

1) The evaluation is for recurrent transient loss of consciousness (TLoC); and
2) A comprehensive evaluation including 30 days of noninvasive ambulatory cardiac monitoring did not demonstrate a cause of the TLoC; and
3) A cardiac arrhythmia is suspected to be the cause of the TLoC; and
4) There is a likely recurrence of the TLoC within the battery longevity of the device.

ICLRs are not a covered service for evaluation of cryptogenic stroke or any other indication.

DIAGNOSTIC GUIDELINE D3, ECHOCARDIOGRAMS WITH CONTRAST FOR CARDIAC CONDITIONS OTHER THAN CARDIAC ANOMALIES

Need for contrast with an echocardiogram should be assessed and, if indicated, implemented at the time of the original ECHO and not as a separate procedure.

DIAGNOSTIC GUIDELINE D4, ADVANCED IMAGING FOR LOW BACK PAIN

In patients with non-specific low back pain and no "red flag" conditions [see Table D4], imaging is not a covered service; otherwise work up is covered as shown in the table. Repeat imaging is only covered when there is a substantial clinical change (e.g. progressive neurological deficit) or new clinical indication for imaging (i.e. development of a new red flag condition). Repeat imaging for acute exacerbations of chronic radiculopathic pain is not covered.

Electromyelography (CPT 96002-4) is not covered for non-specific low back pain.

Table D4
Low Back Pain - Potentially Serious Conditions ("Red Flags") and Recommendations for Initial Diagnostic Work-up

Possible cause	Key features on history or physical examination	Imaging[1]	Additional studies[1]
Cancer	• History of cancer with new onset of LBP	MRI	ESR
	• Unexplained weight loss • Failure to improve after 1 month • Age >50 years • Symptoms such as painless neurologic deficit, night pain or pain increased in supine position	Lumbosacral plain radiography	
	• Multiple risk factors for cancer present	Plain radiography or MRI	
Spinal column infection	• Fever • Intravenous drug use • Recent infection	MRI	ESR and/or CRP
Cauda equina syndrome	• Urinary retention • Motor deficits at multiple levels • Fecal incontinence • Saddle anesthesia	MRI	None
Vertebral compression fracture	• History of osteoporosis • Use of corticosteroids • Older age	Lumbosacral plain radiography	None
Ankylosing spondylitis	• Morning stiffness • Improvement with exercise • Alternating buttock pain • Awakening due to back pain during the second part of the night • Younger age	Anterior-posterior pelvis plain radiography	ESR and/or CRP, HLA-B27
Nerve compression/ disorders (e.g. herniated disc with radiculopathy)	• Back pain with leg pain in an L4, L5, or S1 nerve root distribution present < 1 month • Positive straight-leg-raise test or crossed straight-leg-raise test	None	None
	• Radiculopathic signs[2] present >1 month • Severe/progressive neurologic deficits (such as foot drop), progressive motor weakness	MRI[3]	Consider EMG/NCV
Spinal stenosis	• Radiating leg pain • Older age • Pain usually relieved with sitting (Pseudoclaudication a weak predictor)	None	None
	• Spinal stenosis symptoms present >1 month	MRI[3]	Consider EMG/NCV

[1]Level of evidence for diagnostic evaluation is variable
[2]Radiculopathic signs are defined for the purposes of this guideline as the presence of any of the following:
A) Markedly abnormal reflexes
B) Segmental muscle weakness
C) Segmental sensory loss
D) EMG or NCV evidence of nerve root impingement
E) Cauda equina syndrome,
F) Neurogenic bowel or bladder
G) Long tract abnormalities
[3]Only if patient is a potential candidate for surgery

Red Flag: Red flags are findings from the history and physical examination that may be associated with a higher risk of serious disorders.

CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; NCV = nerve conduction velocity.

Extracted and modified from Chou R, Qaseem A, Snow V, et al: Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007; 147:478-491.

DIAGNOSTIC GUIDELINE D4, ADVANCED IMAGING FOR LOW BACK PAIN (CONT'D)

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

DIAGNOSTIC GUIDELINE D5, NEUROIMAGING FOR HEADACHE

Neuroimaging is not covered in patients with a defined tension or migraine type of headache, or a variation of their usual headache (e.g. more severe, longer in duration, or not responding to drugs).

Neuroimaging is covered for headache when a red flag* is present.
*The following represent red flag conditions for underlying abnormality with headache:

- A) New onset or change in headache in patients who are aged over 50
- B) Thunderclap headache: rapid time to peak headache intensity (seconds to 5 minutes)
- C) Focal neurological symptoms (e.g. limb weakness, lack of coordination, numbness or tingling)
- D) Non-focal neurological symptoms (e.g altered mental status, dizziness)
- E) Abnormal neurological examination
- F) Headache that changes with posture
- G) Headache wakening the patient up (Nota bene migraine is the most frequent cause of morning headache)
- H) Headache precipitated by physical exertion or valsalva maneuver (e.g. coughing, laughing, straining)
- I) Patients with risk factors for cerebral venous sinus thrombosis
- J) Jaw claudication
- K) Nuchal rigidity
- L) New onset headache in a patient with a history of human immunodeficiency virus (HIV) infection
- M) New onset headache in a patient with a history of cancer
- N) Cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), or short-lasting unilateral neuralgiform headache attacks with cranial autonomic features (SUNA).

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

DIAGNOSTIC GUIDELINE D6, BREAST CANCER SCREENING IN ABOVE-AVERAGE RISK WOMEN

Annual screening mammography and annual screening MRI are covered only for women at above-average risk of breast cancer. This coverage, beginning at 30 years of age, includes women who have one or more of the following:

- Greater than 20% lifetime risk of breast cancer
- BRCA1 or BRCA2 gene mutation, or who have not been tested for BRCA but have a first-degree relative who is a BRCA carrier
- A personal history or a first-degree relative diagnosed with Bannayan-Riley-Ruvalcaba syndrome, Cowden syndrome, or Li-Fraumeni syndrome
- Other germline gene mutations known to confer a greater than 20% lifetime risk of breast cancer

For women with a history of high dose chest radiation (≥ 20 Gray) before the age of 30, annual screening MRI and annual screening mammography are covered beginning 8 years after radiation exposure or at age 25, whichever is later.

For women with both a personal history and a family history of breast cancer, annual mammography, annual breast MRI and annual breast ultrasound are covered.

For women with increased breast density, supplemental screening with breast ultrasound, MRI, or digital breast tomosynthesis is not covered.

Breast PET-CT scanning and breast-specific gamma imaging are not covered for breast cancer screening.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

DIAGNOSTIC GUIDELINE D7, NEUROIMAGING IN DEMENTIA

Neuroimaging is covered:

- A) To rule out reversible causes of dementia (tumors, normal pressure hydrocephalus and chronic subdural hematoma) via structural neuroimaging only

Neuroimaging is not covered:

- A) For screening of asymptomatic patients for dementia
- B) To predict progression of the risk of developing dementia in patients with mild cognitive impairment
- C) For screening, diagnosis, or monitoring of dementia, with functional neuroimaging (PET, SPECT or fMRI)

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

DIAGNOSTIC GUIDELINE D8, DIAGNOSTIC TESTING FOR OBSTRUCTIVE SLEEP APNEA (OSA) IN ADULTS

Type I PSG is covered when used to aid the diagnosis of OSA in patients who have clinical signs and symptoms indicative of OSA if performed attended in a sleep lab facility.
OHP clients should have access to least one of the alternatives listed below:

1) Type II or Type III sleep testing devices when used to aid the diagnosis of OSA in patients who have clinical signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.
2) Type IV sleep testing devices measuring three or more channels, one of which is airflow, when used to aid the diagnosis of OSA in patients who have signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.
3) Sleep testing devices measuring three or more channels that include actigraphy, oximetry, and peripheral arterial tone, when used to aid the diagnosis of OSA in patients who have signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.

CPAP titration should be performed as part of the diagnostic study, if possible.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

DIAGNOSTIC GUIDELINE D9, MRI FOR BREAST CANCER DIAGNOSIS

In women with recently diagnosed breast cancer, preoperative or contralateral MRI of the breast is not a covered service.

DIAGNOSTIC GUIDELINE D10, MRI IN MULTIPLE SCLEROSIS

MRI is a diagnostic test for multiple sclerosis and should not be used for routine monitoring of disease.

MRI may be considered in the following circumstances:

A) Suspected drug failure in the setting of clinical relapse in patients with objective changes in neurological status or documented new clinical symptoms such as urinary urgency or cognitive changes
B) Evaluation of a clear objective progression in clinical symptoms in patients with previously relapsing disease to rule out ongoing inflammatory disease when conversion to secondary progressive MS is suspected
C) Patients who require enhanced pharmacovigilance, including
    1) Yearly monitoring for patients treated with natalizumab who are JCV seropositive
    2) One MRI for patients who switch from natalizumab to other therapeutics (including fingolimod, alemtuzumab and dimethyl fumarate) one year after the switch from natalizumab

DIAGNOSTIC GUIDELINE D11, MRI OF THE SPINE (CERVICAL AND THORACIC)

MRI of the cervical and thoracic spine is covered in the following situations:

1) Recent onset of major or progressive neurologic deficit (objective evidence of markedly abnormal reflexes, dermatomal muscle weakness, dermatomal sensory loss, EMG or NCV evidence of nerve root impingement), suspected cauda equina syndrome (loss of bowel or bladder control or saddle anesthesia), or neurogenic claudication in patients who are potential candidates for surgery;
2) Clinical or radiological suspicion of neoplasm; or,
3) Clinical or radiological suspicion of infection.

DIAGNOSTIC GUIDELINE D12, UPPER ENDOSCOPY FOR GERD OR DYSPEPSIA SYMPTOMS

Upper endoscopy for uninvestigated dyspepsia or GERD symptoms is covered for:

Patients less than 50 years of age with persistent symptoms following advice on lifestyle modifications and completion of an appropriate course of twice daily PPI therapy or an H. pylori test and treat protocol.
Patients 50 years of age and older
Patients with "alarm symptoms" including, but not limited to, iron deficiency anemia or weight loss

Upper endoscopy is not covered for patients with previous upper endoscopy with non-malignant findings (other than Barrett's esophagus) in the absence of significant new symptoms.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

DIAGNOSTIC GUIDELINE D13, SCREENING FOR CAROTID ARTERY STENOSIS

Screening for carotid artery stenosis (CPT 93880) in the general primary care population is not a covered service.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

DIAGNOSTIC GUIDELINE D14, LUNG CANCER SCREENING

Low dose computed tomography is included for annual screening for lung cancer in persons aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a

DIAGNOSTIC GUIDELINE D14, LUNG CANCER SCREENING (CONT'D)

person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. Current smokers should be offered evidence based smoking cessation interventions.

DIAGNOSTIC GUIDELINE D15, COMPUTER-AIDED MAMMOGRAPHY

Computer-aided mammography is not intended to be a covered service.

DIAGNOSTIC GUIDELINE D16, OSTEOPOROSIS SCREENING AND MONITORING IN ADULTS

Osteoporosis screening by dual-energy X-ray absorptiometry (DXA) is covered only for women aged 65 or older, and for men or younger women whose 10-year risk of major osteoporotic fracture is equal to or greater than 9.3 percent.

Fracture risk should be assessed by the World Health Organization's FRAX tool or similar instrument.

Routine osteoporosis screening by DXA is not covered for men.

The frequency of subsequent monitoring for development of osteoporosis should not be based on DXA scores alone. If rapid change in bone density is expected, more frequent DXA scanning is appropriate (for example, in patients taking glucocorticoids, those with a history of rapid weight loss, those with medical conditions that could result in secondary osteoporosis, etc.).

If there has been no significant change in an individual's risk factors, monitoring by repeat DXA scanning is covered only at the following frequencies:

- once every two years for those with osteoporosis or advanced osteopenia (T-score of -2.00 or lower)
- once every four years for moderate osteopenia (T-score between -1.50 and -1.99)
- once every ten years for mild osteopenia (T-score between -1.01 and -1.49).
- once every fifteen years for those with normal bone density.

Repeat testing is only covered if the results will influence clinical management. For purposes of monitoring osteoporosis medication therapy, testing at intervals of less than two years is not covered.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

DIAGNOSTIC GUIDELINE D17, PRENATAL GENETIC TESTING

The following types of prenatal genetic testing and genetic counseling are covered for pregnant women:

A) Genetic counseling (CPT 96040, HPCPS S0265) for high risk women who have family history of inheritable disorder or carrier state, ultrasound abnormality, previous pregnancy with aneuploidy, or elevated risk of neural tube defect.
B) Genetic counseling (CPT 96040, HPCPS S0265) prior to consideration of chorionic villus sampling (CVS), amniocentesis, microarray testing, Fragile X, and spinal muscular atrophy screening
C) Validated questionnaire to assess genetic risk in all pregnant women
D) Screening high risk ethnic groups for hemoglobinopathies (CPT 83020, 83021)
E) Screening for aneuploidy with any of five screening strategies [first trimester (nuchal translucency, beta-HCG and PAPP-A), integrated, serum integrated, stepwise sequential, and contingency] (CPT 76813, 76814, 81508-81511)
F) Cell free fetal DNA testing (CPT 81420, 81507) for evaluation of aneuploidy in women who have an elevated risk of a fetus with aneuploidy (maternal age >34, family history or elevated risk based on screening).
G) Ultrasound for structural anomalies between 18 and 20 weeks gestation (CPT 76811, 76812)
H) CVS or amniocentesis (CPT 59000, 59015,82106, 88235, 88267, 88269, 88280, 88285) for a positive aneuploidy screen, maternal age >34, fetal structural anomalies, family history of inheritable chromosomal disorder or elevated risk of neural tube defect.
I) Array CGH (CPT 81228, 81229) when major fetal congenital anomalies are apparent on imaging, or with normal imaging when array CGH would replace karyotyping performed with CVS or amniocentesis in #8 above.
J) FISH testing (CPT 88271, 88275) only if karyotyping is not possible due a need for rapid turnaround for reasons of reproductive decision-making (i.e. at 22w4d gestation or beyond)
K) Screening for Tay-Sachs carrier status (CPT 81255) in high risk populations. First step is hex A, and then additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A
L) Screening for cystic fibrosis carrier status once in a lifetime (CPT 81220-81224)
M) Screening for fragile X status (CPT 81243, 81244) in patients with a personal or family history of
    a. fragile X tremor/ataxia syndrome
    b. premature ovarian failure
    c. unexplained early onset intellectual disability
    d. fragile X intellectual disability
    e. unexplained autism through the pregnant woman's maternal line
N) Screening for spinal muscular atrophy (CPT 81401) once in a lifetime
O) Screening those with Ashkenazi Jewish heritage for Canavan disease (CPT 81200), familial dysautonomia (CPT 81260), and Tay-Sachs carrier status (CPT 81255). Ashkenazi Jewish carrier panel testing (CPT 81412) is covered if the panel would replace and would be of similar or lower cost than individual gene testing including CF carrier testing.
P) Expanded carrier screening only for those genetic conditions identified above

The following genetic screening tests are not covered:

DIAGNOSTIC GUIDELINE D17, PRENATAL GENETIC TESTING (CONT'D)

A) Serum triple screen
B) Screening for thrombophilia in the general population or for recurrent pregnancy loss
C) Expanded carrier screening which includes results for conditions not explicitly recommended for coverage

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

DIAGNOSTIC GUIDELINE D18, ADVANCED IMAGING FOR STAGING OF PROSTATE CANCER

MRI is covered for men with histologically proven prostate cancer if knowledge of the T or N stage could affect management. CT of the pelvis is covered only when MRI is contraindicated.

Radionuclide bone scanning is not covered in men with low risk localized prostate cancer. Low risk is defined as PSA <10 ng/ml and Gleason score <=6 and clinical stage T1-T2a.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

DIAGNOSTIC GUIDELINE D19, SPECT

SPECT (CPT 78451, 78452) is not covered for screening for coronary artery disease in asymptomatic patients.

Stress SPECT (78451, 78452 in conjunction with stress testing) is only covered for diagnosis or risk stratification of coronary artery disease when a stress ECHO is contraindicated, is unavailable or would provide suboptimal imaging (i.e. pre-existing cardiomyopathy, baseline regional wall motion abnormalities, left bundle branch block, paced rhythm, unsuitable acoustic windows due to body habitus, or inability to exercise with inability to utilize dobutamine.)
The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

DIAGNOSTIC GUIDELINE D20, OPHTHALMOLOGY DIAGNOSTIC VISITS

Ophthalmology diagnostic visits (CPT 92002, 92004, 92012, 92014, 92081-92083, 92100, 92140, 92133, 92134) are covered for the evaluation of serious eye symptoms such as sudden vision loss or eye pain.

DIAGNOSTIC GUIDELINE D21, PHARMACOGENETICS TESTING FOR PSYCHIATRIC MEDICATION MANAGEMENT

Pharmacogenetics testing for management of psychiatric medications is not a covered service.

PRACTICE GUIDELINES

GUIDELINE NOTES FOR ANCILLARY AND DIAGNOSTIC SERVICES
NOT APPEARING ON THE JANUARY 1, 2018 PRIORITIZED LIST
OF HEALTH SERVICES

GUIDELINE NOTES FOR HEALTH SERVICES
THAT APPEAR ON THE JANUARY 1, 2018 PRIORITIZED LIST
OF HEALTH SERVICES

GUIDELINE NOTE 1, ROUTINE CERVICAL CANCER SCREENING

Line 3

Cervical cancer screening is covered on Line 3 for women:

Age group in years	Type of screening covered	Frequency
<21	None	Never
21-29	Cytology alone Mandatory HPV testing (87620-87621) is not covered for women age 21-29	Every 3 years
30-65	Co-testing* or cytology alone	Co-testing every 5 years Cytology alone every 3 years
>65	None Unless adequate screening** has not been achieved, or it is <20 years after regression or appropriate management of a high-grade precancerous lesion	Never
Women who have had a hysterectomy with removal of cervix for non cervical cancer related reasons (i.e. other than high grade precancerous lesion, CIN 2 or 3, or cervical cancer)	None	Never
Women who have abnormal testing	Per ASCCP*** Guideline, until indicated to resume routine screening	Per ASCCP Guideline, until indicated to resume routine screening

*Co-testing is defined as simultaneous cytology and mandatory HPV testing.
** Adequate screening is defined as 3 consecutive negative cytology results or 2 consecutive negative HPV results within 10 years of the cessation of screening, with the most recent test occurring within 5 years.
*** American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology guideline (Saslow 2012)

Women who have received a diagnosis of a high-grade precancerous cervical lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised (such as those who are HIV positive) are intended to have screening more frequently than delineated in this guideline.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

GUIDELINE NOTE 2, FETOSCOPIC SURGERY

Line 1

Fetal surgery is only covered for the following conditions: repair of urinary tract obstructions via placement of a urethral shunt, repair of congenital cystic adenomatoid malformation, repair of extralobal pulmonary sequestration, repair of sacrococcygeal teratoma, and therapy for twin-twin transfusion syndrome.

Fetoscopic repair of urinary tract obstruction (S2401) is only covered for placement of a urethral shunt. Fetal surgery for cystic adenomatoid malformation of the lung, extralobal pulmonary sequestration and sacrococcygeal teratoma must show evidence of developing hydrops fetalis.

Certification of laboratory required (76813-76814).

GUIDELINE NOTE 3, PROPHYLACTIC TREATMENT FOR PREVENTION OF BREAST CANCER IN HIGH RISK WOMEN

Line 191

Bilateral prophylactic breast removal and/or oophorectomy are included on Line 191 for women without a personal history of invasive breast cancer who meet the criteria in the NCCN Clinical Practice Guidelines in Oncology. Breast Cancer Risk Reduction. V.1.2016 (2/23/16). www.nccn.org. Prior to surgery, women without a personal history of breast cancer must have a genetics consultation as defined in section A2 of the DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE.

Contralateral prophylactic mastectomy is included on Line 191 for women with a personal history of breast cancer.

GUIDELINE NOTE 4, TOBACCO DEPENDENCE, INCLUDING DURING PREGNANCY

Lines 1,5

Pharmacotherapy (including varenicline, buproprion and all five FDA-approved forms of nicotine-replacement therapy) and behavioral counseling are included on this line, alone or in combination, for at least two quit attempts per year. At least two quit attempts per year

GUIDELINE NOTE 4, TOBACCO DEPENDENCE, INCLUDING DURING PREGNANCY (CONT'D)

must be provided without prior authorization, and each attempt can include both pharmacotherapy and behavioral counseling. Combination drug therapy (i.e. two forms of NRT or NRT plus buproprion) is also included with each quit attempt without prior authorization. However, nicotine inhalers and sprays may be subject to prior authorization.

A minimum of four counseling sessions of at least 10 minutes each (group or individual, telephonic or in person) are included for each quit attempt. More intensive interventions and group therapy are likely to be the most effective behavioral interventions. During pregnancy, additional intensive behavioral counseling is strongly encouraged. All tobacco cessation interventions during pregnancy are not subject to quantity or duration limits.

Inclusion on this line follows the minimum standard criteria as defined in the Oregon Public Health Division "Standard Tobacco Cessation Coverage" (based on the Patient Protection and Affordable Care Act), available here: http://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/TOBACCOPREVENTION/Documents/tob_cessation_coverage_standards.pdf. The USPSTF has also made "A" recommendations for screening, counseling, and treatment of pregnant and nonpregnant adults, included in Guideline Note 106.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

GUIDELINE NOTE 5, OBESITY AND OVERWEIGHT

Line 320

Medical treatment of overweight (with known cardiovascular risk factors) and obesity in adults is limited to intensive counseling on nutrition and physical activity, provided by health care professionals. Intensive counseling is defined as face-to-face contact more than monthly. A multidisciplinary team is preferred, but a single clinician could also deliver intensive counseling in primary care or other settings.

Intensive counseling visits are included on this line for 6 months. Intensive counseling visits may continue for an additional 6 months (up to 12 months) as long as there is evidence of continued weight loss or improvement in cardiovascular risk factors based on the intervention. Maintenance visits at the conclusion of the intensive treatment are included on this line no more than monthly after this intensive counseling period. The characteristics of effective behavioral interventions include: high intensity programs; multicomponent (including at a minimum diet and exercise), group-based commercial programs; Mediterranean diet; and the following sub-elements – calorie counting, contact with a dietician, and comparison to peers.

Known cardiovascular risk factors in overweight persons for which this therapy is effective include: hypertension, dyslipidemia, prediabetes, or the metabolic syndrome.

Medical treatment of obesity in children is limited to comprehensive, intensive behavioral interventions. For treatment of children up to 12 years old, interventions may be targeted only to parents, or to both parents and children.

Pharmacological treatments and devices (e.g. gastric balloons, duodenal jejunal bypass liners, and vagus nerve blocking devices) for obesity are not intended to be included as services on this line or any other line on the Prioritized List.

GUIDELINE NOTE 6, REHABILITATIVE AND HABILITATIVE THERAPIES

Lines 31,46,57,68,71,72,74,81,91,92,131,132,136,150,153,160,178,183,184,196,197,201,202,208,255,257,272,285,287,292,300, 301,309,317,341,345,348,355,356,359,376,377,400,407,415,417,421,422,430,441,453,461,464,465,476,484,495,507,553,556, 569,586,605

The quantitative limits in this guideline note do not apply to mental health or substance abuse conditions.

A total of 30 visits per year of rehabilitative therapy and a total of 30 visits per year of habilitative therapy (physical, occupational and speech therapy) are included on these lines when medically appropriate. Additional visits, not to exceed 30 visits per year of rehabilitative therapy and 30 visits per year of habilitative therapy, may be authorized in cases of a new acute injury, surgery, or other significant change in functional status. Children under age 21 may have additional visits authorized beyond these limits if medically appropriate.

Physical, occupational and speech therapy are only included on these lines when the following criteria are met:

A) therapy is provided by a licensed physical therapist, occupational therapist, speech language pathologist, physician, or other practitioner licensed to provide the therapy,
B) there is objective, measurable documentation of clinically significant progress toward the therapy plan of care goals and objectives,
C) the therapy plan of care requires the skills of a medical provider, and
D) the client and/or caregiver cannot be taught to carry out the therapy regimen independently.

No limits apply while in a skilled nursing facility for the primary purpose of rehabilitation, an inpatient hospital or an inpatient rehabilitation unit.

Spinal cord injuries, traumatic brain injuries, or cerebral vascular accidents are not subject to the visit limitations during the first year after an acute injury.

GUIDELINE NOTE 7, ERYTHROPOIESIS-STIMULATING AGENT (ESA) GUIDELINE

Lines 12,59,93,95,112-116,126,133,135,157,158,161,163,179,191,200,201,209,211,215,216,218,230,235,238,239,259-263,271, 276,286-288,294,295,314-316,329,396,397,400,418,433,556,589

A) Indicated for anemia (Hgb < 10gm/dl or Hct < 30%) induced by cancer chemotherapy given within the previous 8 weeks or in the setting of myelodysplasia.
   1) Reassessment should be made after 8 weeks of treatment. If no response, treatment should be discontinued. If response is demonstrated, ESAs should be discontinued once the hemoglobin level reaches 10, unless a lower hemoglobin level is sufficient to avoid the need for red blood cell (RBC) transfusion.
B) Indicated for anemia (Hgb < 10gm/dl or HCT < 30%) associated with HIV/AIDS.
   1) An endogenous erythropoietin level < 500 IU/L is required for treatment, and patient may not be receiving zidovudine (AZT) > 4200 mg/week.
   2) Reassessment should be made after 8 weeks. If no response, treatment should be discontinued. If response is demonstrated, the lowest ESA dose sufficient to reduce the need for RBC transfusions should be used, and the Hgb should not exceed 11gm/dl.
C) Indicated for anemia (Hgb < 10 gm/dl or HCT <30%) associated with chronic renal failure, with or without dialysis.
   1) Reassessment should be made after 12 weeks. If no response, treatment should be discontinued. If response is demonstrated, the lowest ESA dose sufficient to reduce the need for RBC transfusions should be used, and the Hgb should not exceed 11gm/dl. In those not on dialysis, the Hgb level should not exceed 10gm/dl.

GUIDELINE NOTE 8, BARIATRIC SURGERY

Line 320

Bariatric/metabolic surgery (limited to Roux-en-Y gastric bypass, and sleeve gastrectomy) is included on Line 320 when the following criteria are met:

A) Age ≥ 18
B) The patient has obesity with a:
   1) BMI ≥ 40 OR
   2) BMI ≥ 35 with:
      a) Type 2 diabetes, OR
      b) at least two of the following other serious obesity-related comorbidities: hypertension, coronary heart disease, mechanical arthropathy in major weight bearing joint, sleep apnea
C) Repeat bariatric surgery is included when it is a conversion from a less intensive (such as gastric band or sleeve gastrectomy) to a more intensive surgery (e.g. Roux-en-Y). Repair of surgical complications (excluding failure to lose sufficient weight) are also included on this and other lines. Reversal of surgical procedures and devices is included on this line when benefits of reversal outweigh harms.
D) Participate in the following four evaluations and meet criteria as described.
   1) Psychosocial evaluation: (Conducted by a licensed mental health professional)
      a) Evaluation to assess potential compliance with post-operative requirements.
      b) Must remain free of abuse of or dependence on alcohol during the six-month period immediately preceding surgery. No current use of any nicotine product or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within 1 month of the quit date and within 1 month of the surgery to confirm abstinence from illicit drugs. Tobacco and nicotine abstinence to be confirmed in active users by negative cotinine levels at least 6 months apart, with the second test within one month of the surgery date.
      c) No mental or behavioral disorder that may interfere with postoperative outcomes[1].
      d) Patient with psychiatric illness must be stable for at least 6 months.
   2) Medical evaluation: (Conducted by OHP primary care provider)
      a) Pre-operative physical condition and mortality risk assessed with patient found to be an appropriate candidate.
      b) Optimize medical control of diabetes, hypertension, or other co-morbid conditions.
      c) Female patient not currently pregnant with no plans for pregnancy for at least 2 years post-surgery. Contraception methods reviewed with patient agreement to use effective contraception through 2nd year post-surgery.
   3) Surgical evaluation: (Conducted by a licensed bariatric surgeon associated with program[2])
      a) Patient found to be an appropriate candidate for surgery at initial evaluation and throughout period leading to surgery.
      b) Received counseling by a credentialed expert on the team regarding the risks and benefits of the procedure and understands the many potential complications of the surgery (including death) and the realistic expectations of post-surgical outcomes.
   4) Dietician evaluation: (Conducted by licensed dietician)
      a) Evaluation of adequacy of prior dietary efforts to lose weight. If no or inadequate prior dietary effort to lose weight, must undergo six-month clinically supervised weight reduction program (including intensive nutrition and physical activity counseling as defined by the USPSTF).
      b) Counseling in dietary lifestyle changes
E) Participate in additional evaluations:
   1) Post-surgical attention to lifestyle, an exercise program and dietary changes and understands the need for post-surgical follow-up with all applicable professionals (e.g. nutritionist, psychologist/psychiatrist, exercise physiologist or physical therapist, support group participation, regularly scheduled physician follow-up visits).

[1] Many patients (>50%) have depression as a co-morbid diagnosis that, if treated, would not preclude their participation in the bariatric surgery program.

GUIDELINE NOTE 8, BARIATRIC SURGERY (CONT'D)

[2] All surgical services must be provided by a program with current accreditation (as a comprehensive center or low acuity center) by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP)

GUIDELINE NOTE 9, WIRELESS CAPSULE ENDOSCOPY

Lines 29,56

A) Wireless capsule endoscopy is included on these lines for diagnosis of:
   1) Obscure GI bleeding suspected to be of small bowel origin with iron deficiency anemia or documented GI blood loss
   2) Suspected Crohn's disease with prior negative work up
B) Wireless capsule endoscopy is not included on these lines for:
   1) Colorectal cancer screening
   2) Confirmation of lesions of pathology normally within the reach of upper or lower endoscopes (lesions proximal to the ligament of Treitz or distal to the ileum)
C) Wireless capsule endoscopy is only included on these lines when the following conditions have been met:
   1) Prior studies must have been performed and been non-diagnostic
      a) GI bleeding: upper and lower endoscopy
      b) Suspected Crohn's disease: upper and lower endoscopy, small bowel follow through
   2) Radiological evidence of lack of stricture
   3) Only covered once during any episode of illness
   4) FDA approved devices must be used
   5) Patency capsule should not be used prior to procedure

GUIDELINE NOTE 10, CENTRAL SEROUS CHORIORETINOPATHY AND POSTERIOR CYCLITIS

Lines 360,383

Central serous chorioretinopathy (ICD-10-CM H35.71) is included on Line 383 only for treatment when the condition has been present for three months or longer. Posterior Cyclitis (ICD-10-CM H30.2) should only be treated in patients with 20/40 or worse vision.

GUIDELINE NOTE 11, COLONY STIMULATING FACTOR (CSF) GUIDELINES

Lines 93,95,112-116,126,133,135,157,158,161,163,179,191,200,201,209,211,215,216,218,230,235,238,239,259-263,271,276, 286-288,294,314-316,329,396,397,400,418,433,556,589

A) CSF are not indicated for primary prophylaxis of febrile neutropenia unless the primary chemotherapeutic regimen is known to produce febrile neutropenia at least 20% of the time. CSF should be considered when the primary chemotherapeutic regimen is known to produce febrile neutropenia 10-20% of the time; however, if the risk is due to the chemotherapy regimen, other alternatives such as the use of less myelosuppressive chemotherapy or dose reduction should be explored in this situation.
B) For secondary prophylaxis, dose reduction should be considered the primary therapeutic option after an episode of severe or febrile neutropenia except in the setting of curable tumors (e.g., germ cell), as no disease free or overall survival benefits have been documented using dose maintenance and CSF.
C) CSF are not indicated in patients who are acutely neutropenic but afebrile.
D) CSF are not indicated in the treatment of febrile neutropenia except in patients who received prophylactic filgrastim or sargramostim or in high risk patients who did not receive prophylactic CSF. High risk patients include those age >65 years or with sepsis, severe neutropenia with absolute neutrophil count <100/mcl, neutropenia expected to be more than 10 days in duration, pneumonia, invasive fungal infection, other clinically documented infections, hospitalization at time of fever, or prior episode of febrile neutropenia.
E) CSF are not indicated to increase chemotherapy dose-intensity or schedule, except in cases where improved outcome from such increased intensity has been documented in a clinical trial.
F) CSF (other than pegfilgrastrim) are indicated in the setting of autologous progenitor cell transplantation, to mobilize peripheral blood progenitor cells, and after their infusion.
G) CSF are NOT indicated in patients receiving concomitant chemotherapy and radiation therapy.
H) There is no evidence of clinical benefit in the routine, continuous use of CSF in myelodysplastic syndromes. CSF may be indicated for some patients with severe neutropenia and recurrent infections, but should be used only if significant response is documented.
I) CSF is indicated for treatment of cyclic, congenital and idiopathic neutropenia.

GUIDELINE NOTE 12, TREATMENT OF CANCER WITH LITTLE OR NO BENEFIT

Lines 93,112-116,125,129,133,135,157,158,163,179,191,200,201,209,211,215,216,218,230,235,238,239,259-263,271,276,286, 287,294,314-316,329,372,396,397,418,433,589,600

Cancer is a complex group of diseases with treatments that vary depending on the specific subtype of cancer and the patient's unique medical and social situation. Goals of appropriate cancer therapy can vary from intent to cure, disease burden reduction, disease stabilization and control of symptoms. Cancer care must always take place in the context of the patient's support systems, overall heath, and core values. Patients should have access to appropriate peer-reviewed clinical trials of cancer therapies. A comprehensive multidisciplinary approach to treatment should be offered including palliative care services (see STATEMENT OF INTENT 1, PALLIATIVE CARE).

Treatment with intent to prolong survival is not a covered service for patients who have progressive metastatic cancer with

GUIDELINE NOTE 12, TREATMENT OF CANCER WITH LITTLE OR NO BENEFIT (CONT'D)

A) Severe co-morbidities unrelated to the cancer that result in significant impairment in two or more major organ systems which would affect efficacy and/or toxicity of therapy; OR
B) A continued decline in spite of best available therapy with a non reversible Karnofsky Performance Status or Palliative Performance score of <50% with ECOG performance status of 3 or higher which are not due to a pre-existing disability.

Treatments with intent to relieve symptoms or improve quality of life are covered as defined in STATEMENT OF INTENT 1, PALLIATIVE CARE.
Examples include:
A) Single-dose radiation therapy for painful bone metastases with the intent to relieve pain and improve quality of life.
B) Surgical decompression for malignant bowel obstruction.
C) Medication therapy such as chemotherapy with low toxicity/low side effect agents with the goal to decrease pain from bulky disease or other identified complications. Cost of chemotherapy and alternative medication(s) should also be considered.

To qualify for treatment coverage, the cancer patient must have a documented discussion about treatment goals, treatment prognosis and the side effects, and knowledge of the realistic expectations of treatment efficacy. This discussion may take place with the patient's oncologist, primary care provider, or other health care provider, but preferably in a collaborative interdisciplinary care coordination discussion. Treatment must be provided via evidence-driven pathways (such as NCCN, ASCO, ASH, ASBMT, or NIH Guidelines) when available.

GUIDELINE NOTE 13, HEMANGIOMAS, COMPLICATED

Lines 321,625

Dermatologic hemangiomas (ICD-10-CM D18.01 Hemangioma and Lymphangioma of skin and subcutaneous tissue) are included on Line 321 when they are ulcerated, infected, recurrently hemorrhaging, or function-threatening (e.g. eyelid hemangioma). Otherwise, they are included on Line 625.

GUIDELINE NOTE 14, SECOND BONE MARROW TRANSPLANTS

Lines 95,114,116,130,163,179,218,261,288

Second bone marrow transplants are not covered except for tandem autologous transplants for multiple myeloma.

GUIDELINE NOTE 15, HETEROTOPIC BONE FORMATION

Lines 81,356

Radiation treatment is indicated only in those at high risk of heterotopic bone formation: those with a history of prior heterotopic bone formation, ankylosing spondylitis or hypertrophic osteoarthritis.

GUIDELINE NOTE 16, PROTON BEAM THERAPY FOR CANCER

Lines 93,113,126,129,191,201,238,276,287,294,372,396,397

Proton beam therapy is included on Lines 113 CANCER OF EYE AND ORBIT, 126 BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD and 294 CANCER OF BRAIN AND NERVOUS SYSTEM.

Proton beam therapy is included on Lines 129, 201 and 287 only for: malignant skull base, paranasal sinus (including lethal midline granuloma), spinal, and juxtaspinal tumors .

Proton beam therapy is additionally included on Lines 93, 191, 238, 276, 396 and 397 only for pediatric malignant tumors (incident cancer under age 21.)

GUIDELINE NOTE 17, PREVENTIVE DENTAL CARE

Lines 3,53

Dental cleaning is limited to once per 12 months for adults and twice per 12 months for children up to age 19 (D1110, D1120). More frequent dental cleanings may be required for certain higher risk populations.

Fluoride varnish (99188) is included on Line 3 for use with children 18 and younger during well child preventive care visits. Fluoride treatments (D1206 and D1208) are included on Line 53 PREVENTIVE DENTAL SERVICES for use with adults and children during dental visits. The total number of fluoride applications provided in all settings is not to exceed four per twelve months for a child at high risk for dental caries and two per twelve months for a child not at high risk. The number of fluoride treatments is limited to once per 12 months for average risk adults and up to four times per 12 months for high risk adults.

GUIDELINE NOTE 18, VENTRICULAR ASSIST DEVICES

Lines 82,98,264

Ventricular assist devices are covered as a bridge to cardiac transplant; as treatment for pulmonary hypertension when pulmonary hypertension is the only contraindication to cardiac transplant and the anticipated outcome is cardiac transplant; as a bridge to recovery; or as destination therapy.

When used as destination therapy, patients must

A) have chronic end-stage heart failure (New York Heart Association Class IIIB or IV end-stage left ventricular failure) for more than 60 days, AND
B) not be a candidate for heart transplantation, AND
C) meet all of the following conditions:
    1) Have failed to respond to optimal medical management, including beta-blockers and ACE inhibitors (if tolerated) for at least 45 of the last 60 days, or have been balloon pump dependent for 7 days, or IV inotrope dependent for 14 days; and
    2) Have a left ventricular ejection fraction (LVEF) <25%; and
    3) Have demonstrated functional limitation with a peak oxygen consumption of <14 ml/kg/min unless balloon pump or inotrope dependent or physically unable to perform the test.
D) Have adequate psychological condition and appropriate external psychosocial support for prolonged VAD support
E) Have adequate end organ function

GUIDELINE NOTE 19, PET SCAN GUIDELINES

Lines 113,116,133,135,157,158,163,174,200,201,211,230,260,263,276,287,314

PET Scans are covered for diagnosis of the following cancers only:
- Solitary pulmonary nodules and non-small cell lung cancer
- Evaluation of cervical lymph node metastases when CT or MRI do not demonstrate an obvious primary tumor.

For diagnosis, PET is covered only when it will avoid an invasive diagnostic procedure, or will assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

PET scans are covered for the initial staging of the following cancers:
- Cervical cancer only when initial MRI or CT is negative for extra-pelvic metastasis
- Head and neck cancer when initial MRI or CT is equivocal
- Colon cancer
- Esophageal cancer
- Solitary pulmonary nodule
- Non-small cell lung cancer
- Lymphoma
- Melanoma

For staging, PET is covered when clinical management of the patient will differ depending on the stage of the cancer identified and either:

A) the stage of the cancer remains in doubt after standard diagnostic work up, OR
B) PET replaces one or more conventional imaging studies when they are insufficient for clinical management of the patient.

Restaging is covered only for cancers for which staging is covered and for thyroid cancer if recurrence is suspected and I131 scintography is negative. For restaging, PET is covered after completion of treatment for the purpose of detecting residual disease, for detecting suspected recurrence or to determine the extent of a known recurrence. PET is not covered to monitor tumor response during the planned course of therapy. PET scans are NOT indicated for routine follow up of cancer treatment or routine surveillance in asymptomatic patients.

PET scans are also indicated for preoperative evaluation of the brain in patients who have intractable seizures and are candidates for focal surgery. PET scans are NOT indicated for cardiac evaluation.

GUIDELINE NOTE 20, ATTENTION DEFICIT/HYPERACTIVITY DISORDERS IN CHILDREN

Line 122

Use of ICD-10-CM F90.9, Attention deficit/hyperactivity disorder, unspecified type, in children age 5 and under, is appropriate only when the following apply:

- Child does not meet the full criteria for the full diagnosis because of their age.
- For children age 3 and under, when the child exhibits functional impairment due to hyperactivity that is clearly in excess of the normal activity range for age (confirmed by the evaluating clinician's observation, not only the parent/caregiver report), and when the child is very limited in his/her ability to have the sustained periods of calm, focused activity which would be expected for the child's age.

For children age 5 and under diagnosed with disruptive behavior disorders, including those at risk for ADHD, first line therapy is evidence-based, structured "parent-behavior training. Second line therapy is pharmacotherapy.

GUIDELINE NOTE 20, ATTENTION DEFICIT/HYPERACTIVITY DISORDERS IN CHILDREN (CONT'D)

For children age 6 and over who are diagnosed with ADHD, pharmacotherapy alone or pharmacotherapy with psychosocial/behavioral treatment are included on this line for first line therapy.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

GUIDELINE NOTE 21, SEVERE INFLAMMATORY SKIN DISEASE

Lines 424,480,502,530,539,654

Inflammatory skin conditions included in this guideline are:
A) Psoriasis
B) Atopic dermatitis
C) Lichen planus
D) Darier disease
E) Pityriasis rubra pilaris
F) Discoid lupus

The conditions above are included on line 424 if severe, defined as having functional impairment (e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) AND one or more of the following:
A) At least 10% of body surface area involved
B) Hand, foot or mucous membrane involvement.

Otherwise, these conditions above are included on Lines 480, 502, 530, 539 and 654.

For severe psoriasis, first line agents include topical agents, phototherapy and methotrexate. Second line agents include other systemic agents and oral retinoids and should be limited to those who fail, or have contraindications to, or do not have access to first line agents. Biologics are included on this line only for the indication of severe plaque psoriasis; after documented failure of first line agents and failure of (or contraindications to) a second line agent.

For severe atopic dermatitis/eczema, fist line agents include topical corticosteroids, narrowband UVB, cyclosporine, methotrexate, and azathioprine. Second line agents include topical pimecrolimus and topical tacrolimus and should be limited to those who fail or have contraindications to first line agents. Biologic agents are included on this line for atopic dermatitis only after failure of or contraindications to first and second line agents.

GUIDELINE NOTE 22, PLANNED CESAREAN DELIVERY

Line 1

Cesarean delivery on maternal request without medical or obstetrical indication is not included on this line (or the list). Planned cesarean delivery is also not included on this line (or the list) for: small for gestational age; suspected cephalopelvic disproportion; maternal Hepatitis B infection; or maternal Hepatitis C infection.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

GUIDELINE NOTE 23, COLON CANCER SURVEILLANCE

Line 157

A) History and physical exam is indicated every 3 to 6 months for the first three years after primary therapy, then annually thereafter.
B) CEA testing should be performed every 2-3 months after colon resection for at least two years in patients with stage II or III disease for whom resection of liver metastases is clinically indicated
C) Colonoscopy is indicated every 3 to 5 years.
D) No other surveillance testing is indicated.

GUIDELINE NOTE 24, COMPLICATED HERNIAS

Lines 168,522

Complicated hernias are included on Line 168 if they cause symptoms of intestinal obstruction and/or strangulation. Incarcerated hernias (defined as non-reducible by physical manipulation) are also included on Line 168, excluding incarcerated ventral hernias. Incarcerated ventral hernias are included on Line 522, because the chronic incarceration of large ventral hernias does not place the patient at risk for impending strangulation.

GUIDELINE NOTE 25, STEM CELL TRANSPLANTATION FOR NEUROBLASTOMA

Line 260

Stem cell transplantation (CPT 38204-38215, 38230-38241) is only included on this line for treatment of high risk neuroblastoma (ICD-10-CM C74).

GUIDELINE NOTE 26, BREAST CANCER SURVEILLANCE

Line 191

A) History and physical exam is indicated every 3 to 6 months for the first three years after primary therapy, then every 6-12 months for the next 2 years, then annually thereafter.
B) Mammography is indicated annually, and patients treated with breast conserving therapy, initial mammogram of the affected breast should be 6 months after completion of radiotherapy.
C) No other surveillance testing is indicated.

GUIDELINE NOTE 27, SLEEP APNEA

Line 203

CPAP is covered initially when all of the following conditions are met:

- 12 week 'trial' period to determine benefit. This period is covered if apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) is greater than or equal to 15 events per hour; or if between 5 and 14 events with additional symptoms including one or more of the following:
    - excessive daytime sleepiness defined as either an Epworth Sleepiness Scale score>10 or daytime sleepiness interfering with ADLs that is not attributable to another modifiable sedating condition (e.g. narcotic dependence), or
    - documented hypertension, or
    - ischemic heart disease, or
    - history of stroke;
- Providers must provide education to patients and caregivers prior to use of CPAP machine to ensure proper use; and
- Positive diagnosis through polysomnogram (PSG) or Home Sleep Test (HST).

CPAP coverage subsequent to the initial 12 weeks is based on documented patient tolerance, compliance, and clinical benefit. Compliance (adherence to therapy) is defined as use of CPAP for at least four hours per night on 70% of the nights during a consecutive 30-day period.

Mandibular advancement devices (oral appliances) are covered for those for whom CPAP fails or is contraindicated.

Surgery for sleep apnea in adults is not included on this line (due to lack of evidence of efficacy). Surgical codes are included on this line only for children who meet criteria according to Guideline Note 118 OBSTRUCTIVE SLEEP APNEA DIAGNOSIS AND TREATMENT FOR CHILDREN.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

GUIDELINE NOTE 28, TROCHANTERIC BURSITIS

Lines 376,503

Trochanteric bursitis (ICD-10-CM M70.6 and M70.7) is included on Line 376 for pairing with physical therapy and steroid joint injections. Trochanteric bursitis is included on Line 503 for pairing with surgical interventions (i.e. CPT 27062).

GUIDELINE NOTE 29, TYMPANOSTOMY TUBES IN ACUTE OTITIS MEDIA

Line 389

Tympanostomy tubes (CPT 69436) are only included on this line as treatment for:

A) recurrent acute otitis media (three or more well-documented and separate episodes in six months or four or more well-documented and separate episodes in the past 12 months with at least one episode in the past six months) in patients who have unilateral or bilateral middle ear effusion at the time of assessment for tube candidacy, or
B) patients with complicating conditions (immunocompromised host, meningitis by lumbar puncture, acute mastoiditis, sigmoid sinus/jugular vein thrombosis by CT/MRI/MRA, cranial nerve paralysis, sudden onset dizziness/vertigo, need for middle ear culture, labyrinthitis, or brain abscess).

Patients with craniofacial anomalies, Down's syndrome, cleft palate, permanent hearing loss of 25dB or greater independent of otitis media with effusion, and patients with speech and language delay may be considered for tympanostomy if unresponsive to appropriate medical treatment or having recurring infections (without needing to meet the strict "recurrent" definition above).

Removal of retained tympanostomy tubes requiring anesthesia (CPT code 69424) or as an office visit, is included on Line 422 as a complication, pairing with ICD-10-CM H74.8.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

000166 C2C DIAR_C0000012018 04-24-2019

COVER SHEET

QIC DME 31

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April 16, 2019

VIA PRIORITY MAIL

C2C Innovative Solutions, Inc.
Attn: DME Qualified Independent Contractor (QIC)
P.O. Box 44013
Jacksonville, FL 32231-4013

Received
C2C Mailroom
APR 22 2019
QA# MR117
C2C Solutions, Inc.

Re: Request for Reconsideration
Patient: David Christenson
Medicare ID: 7QR9QM0QP33
Date of Service: 11/3/18; 12/3/18; 1/3/19
Device: E0766 KFRR (TTFT)
Supplier: Novocure, Inc.
Contractor: CGS Jurisdiction B
Our Ref: 19-296 Rec.

Dear C2C Innovative Solutions, Inc.:

On behalf of Mr. David Christenson, we hereby appeal CGS's denial of the Optune system, E0766, an FDA-approved device that treats individuals diagnosed with glioblastoma, an aggressive malignant brain cancer with few treatment options. In addition to surgery, chemotherapy, and radiation, Mr. Christenson's provider prescribed the Optune system. The contractor denied the claims, stating that "the currently published studies in the medical literature do not clearly document the effectiveness of this device." LCD L34823 is generally referenced. For the reasons outlined below, the LCD should not be deferred to for Mr. Christenson.

Contrary to the contractor's statements, the device is reasonable and necessary. The published literature supports the effectiveness of the device:

- The final analysis of the randomized phase 3 trial (695 patients) found that the addition of Optune to standard chemotherapy treatment "resulted in statistically significant improvement in progression-free survival and overall survival" over patients that were treated with chemotherapy alone. Stupp et al. at 2315 (JAMA 2017). See also, interim analysis of 315 patients from this study (adding Optune to maintenance chemotherapy "significantly prolonged progression-free and overall survival"). Stupp et al. at 2542 (JAMA 2015).

In fact, the data monitoring safety board of the EF-14 trial recommended early termination of the study to allow patients who were not receiving the device to cross over to the treatment arm and receive the Optune device, deeming it unethical to withhold it from patients in the control arm. The FDA agreed. The study included the outcomes for both newly diagnosed and recurrent

patients. The device is incorporated in the NCCN guidelines, considered the gold standard for cancer care. Based on the strength of the peer-reviewed literature and the lack of medical alternatives, the Optune system has been certified at more than 800 cancer treatment centers, and has been prescribed by over 1200 physicians in 50 states, the District of Columbia, and Puerto Rico, for over 7200 patients.

The QIC is not bound by the LCD. Prior QIC decisions have made the following bolded statements which are addressed below.

A. "The medical documentation in support of efficacy is not within the usual scope and breadth of current medical literature with peer acknowledgement and review."

Respectfully, the sentence and logic are difficult to follow. In terms of the breadth and scope of the peer-reviewed literature, a PubMed search reveals over 100 peer-reviewed articles ranging from randomized controlled trials, to case reports, to meta-analyses. The scope and breadth are particularly remarkable given the orphan status of the disease. In the past 10 years, TTFT was the only positive clinical trial and breakthrough treatment in glioblastoma. The pivotal studies were published in the Journal of the American Medical Association (JAMA), one of the most prestigious journals in the United States and one of the most cited journals in the world. Certainly, in view of the number of publications and the prestigious peer-reviewed articles that exist, it is difficult to understand the QIC's assertion that the studies do not have peer acknowledgement and review. Further, the peer-reviewed literature was and is so strong, that TTFT has been incorporated in the NCCN guidelines. Finally, based on the strength of the outcomes seen, the Data Safety Monitoring Board (DSMB) recommended early termination of the clinical trial so that those in the control arm of the clinical trial could cross over and receive treatment. This was so because it would have been unethical to withhold this life-saving treatment from the control group. Thus, the effectiveness of the treatment certainly enjoyed the "acknowledgement and review" of the DSMB and the FDA.

B. "More specifically, the QIC has reviewed the peer reviewed and evidence based literature relative to clinical trials for TTFT, and has found the literature and clinical trials to be limited in number and the clinicals trial not non-biased; that is, the clinical trials were not independent, but funded by Novocure."

Again, respectfully, the sentence and logic are difficult to follow. As noted above, GBM is an orphan disease with a difficult prognosis. More than one randomized controlled clinical trial was performed and reported in the peer-reviewed literature and more than 50 articles regarding TTFT for glioblastoma have been reported in the peer-reviewed literature. One of the seminal clinical trials resulted in multiple publications in the Journal of the American Medical Association, one of the most prestigious journals in the United States. On March 6, 2019, the Contractor Advisory Committee (CAC) recommended Medicare coverage of TTFT.[1] The experts found that the peer-reviewed literature shows the treatment is safe and effective. The experts did not find that the studies were limited in number or biased.

[1] See https://med.noridianmedicare.com/web/jddme/policies/lcd/contractor-advisory-committee.

With respect to the "not non-biased" assertion, it is unclear if the QIC is attempting to assert that the manufacturer's funding of the clinical trials resulted in biased publications that could not support Medicare coverage. The studies were conducted at some of the most prestigious academic institutions in the United States by academic researchers. Most of the published clinical research on a medical intervention is sponsored in the United States. Indeed, Medicare often requires industry to sponsor certain studies as a condition of Medicare coverage. A cursory review of the literature supporting most LCDs shows that they are industry-sponsored studies. Industry sponsorship does not make a peer-reviewed study, written by academic authors, "not non-biased" such that the study cannot support Medicare coverage. If such a standard applied, Medicare would be precluded from considering most of the peer-reviewed literature published with respect to a technological advancement – an absurd result.

With respect to the number of clinical trials, Appellant notes that GBM is an orphan disease with a high mortality rate. Because the treatment is so effective, the FDA deemed it unethical to continue a study that withheld such an effective treatment from those battling a fatal disease. This is consistent with the Declaration of Helsinki, paragraph 18.[2] The CAC recognized that just as the FDA deemed it unethical to continue the clinical trial, it would be unethical to even begin more clinical studies which involved withholding a proven effective treatment for a fatal disease. A "limited number" of clinical trials is common when a treatment is proven so effective for a fatal condition. After the first study determining that a tourniquet is an effective treatment to prevent people from dying from arterial bleeding, ethically, a second study cannot be conducted. Likewise, with TTFT, given the conclusive effectiveness, additional trials that withhold the treatment cannot be conducted ethically.

Please overturn the contractor's denial of the claims at issue given the strength of the literature, rarity of the disease, limited treatment options for patients like Mr. Christenson, and other evidence supporting the effectiveness of the device. If you have any questions regarding this reconsideration request, please do not hesitate to contact me at (412) 561-6250.

Yours very truly,

Debra M. Parrish
788 Washington Road
Pittsburgh, PA 15228

(continued on next page)

[2] See World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects: "When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study." The Declaration of Helsinki finds its roots in the Nuremberg Code which required informed consent for human clinical trials after the horrific experiments conducted in concentration camps during WWII. The quoted section has been interpreted to preclude continuation of a clinical trial when effectiveness has been established for a fatal illness.

Enclosures:

Attachment A:	Appointment of Representative Form
Attachment B:	CD of Supporting Documents (v.18)
Attachment C:	Additional Medical Record
Attachment D:	Redetermination Decision

cc: Mr. David Christenson
5754 Clevedon Ln.
Oshkosh, WI 54904

Novocure, Inc.

ATTACHMENT A

TO THE RECONSIDERATION REQUEST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR MEDICARE & MEDICAID SERVICES

Form Approved
OMB No. 0938-0950

APPOINTMENT OF REPRESENTATIVE

NAME OF PARTY	MEDICARE OR NATIONAL PROVIDER IDENTIFIER NUMBER
David Christenson	7QR9QM0QP33

SECTION I: APPOINTMENT OF REPRESENTATIVE

To be completed by the party seeking representation (i.e., the Medicare beneficiary, the provider or the supplier):

I appoint this individual: Debra M. Parrish to act as my representative in connection with my claim or asserted right under Title XVIII of the Social Security Act (the "Act") and related provisions of Title XI of the Act. I authorize this individual to make any request; to present or to elicit evidence; to obtain appeals information; and to receive any notice in connection with my appeal, wholly in my stead. I understand that personal medical information related to my appeal may be disclosed to the representative indicated below.

SIGNATURE OF PARTY SEEKING REPRESENTATION		DATE
David Christenson		1/26/2019
STREET ADDRESS		PHONE NUMBER (with Area Code)
5754 Clevedon Lane		(920) 203-5636
CITY	STATE	ZIP
Oshkosh	WI	54904

SECTION II: ACCEPTANCE OF APPOINTMENT

To be completed by the representative:

I, Debra M. Parrish, hereby accept the above appointment. I certify that I have not been disqualified, suspended, or prohibited from practice before the Department of Health and Human Services; that I am not, as a current or former employee of the United States, disqualified from acting as the party's representative; and that I recognize that any fee may be subject to review and approval by the Secretary.

I am a / an ATTORNEY (Debra M. Parrish)

(PROFESSIONAL STATUS OR RELATIONSHIP TO THE PARTY, E.G. ATTORNEY, RELATIVE, ETC.)

SIGNATURE OF REPRESENTATIVE		DATE
		2-5-19
STREET ADDRESS		PHONE NUMBER (with Area Code)
788 Washington Road		(412)561-6250
CITY	STATE	ZIP
Pittsburgh	PA	15228

SECTION III: WAIVER OF FEE FOR REPRESENTATION

Instructions: This section must be completed if the representative is required to, or chooses to waive their fee for representation. (Note that providers or suppliers that are representing a beneficiary and furnished the items or services may not charge a fee for representation and **must** complete this section.)

I waive my right to charge and collect a fee for representing ______________________ before the Secretary of the Department of Health and Human Services.

SIGNATURE	DATE

SECTION IV: WAIVER OF PAYMENT FOR ITEMS OR SERVICES AT ISSUE

Instructions: Providers or suppliers serving as a representative for a beneficiary to whom they provided items or services must complete this section if the appeal involves a question of liability under section 1879(a)(2) of the Act. (Section 1879(a)(2) generally addresses whether a provider/supplier or beneficiary did not know, or could not reasonably be expected to know, that the items or services at issue would not be covered by Medicare.)

I waive my right to collect payment from the beneficiary for the items or services at issue in this appeal if a determination of liability under §1879(a)(2) of the Act is at issue.

SIGNATURE	DATE

Form CMS-1696 (10/10)

ATTACHMENT B

TO THE RECONSIDERATION REQUEST

ATTACHMENT C

TO THE RECONSIDERATION REQUEST

ASCENSION NE WI ST. ELIZABETH HOSPITAL, APPLETON, WI
RADIATION ONCOLOGY

PATIENT NAME: CHRISTENSON, DAVID P ADMIT DATE: 09/19/18
PROVIDER: DAVIS MD, RICK D REPORT NO: 0922-0008

DATE OF SERVICE: 09/19/2018

FOLLOWUP NOTE FROM RADIATION ONCOLOGY CLINIC

REFERRING PHYSICIAN: Karen Gremminger, M.D.

DIAGNOSIS: Glioblastoma of the right occipital lobe. Grade is IV. Stage is not applicable. The patient's radiation therapy delivered included VMAT and IMRT to the brain on 08/17/2015, received 6000 cGy in 30 fractions, 200 cGy each, completed that on 09/28/2015. He later received a single fraction SRS within the right occipital tumor bed receiving 24 Gy in a single fraction on 01/13/2016. Currently, he is on optimum therapy. Previous visit was 06/27/2018.

INTERVAL HISTORY: The patient has had no change in his clinical status. He has no new neurologic status, no side effects. He continues to wear his Optune roughly 18 hours a day or more. They do receive updates on compliance from the Optune therapy company. An MRI of the brain done on 09/18/2018, showed stable postoperative findings. No evidence of tumor recurrence or progression. No change in T2-FLAIR signal.

REVIEWED MEDICATIONS: He is on Decadron 1 mg a day, aspirin, docusate sodium, Coumadin and acetaminophen as needed.

ALLERGIES: NO KNOWN ALLERGIES.

REVIEW OF SYSTEMS: Complete 12 system review done and intake reviewed with the patient and updated the record as needed. Pain is 0/10. Remainder of his review of systems is within normal limits. ECOG status is 0. Advanced directives completed and in place.

PHYSICAL EXAMINATION: Age appropriate male. He is wearing his Optune device on his head with associated wires and pads. Otherwise, no significant irregularities in the patient. His height is 76 inches, weight is 228 pounds. BMI is 27.8. He is appropriately counseled about this. Temperature 98.1, heart rate 56, respiratory rate is 16, blood pressure 130/60, O2 sat 97%. Brief survey of neurologic function and cranial nerves are normal. He has no abnormalities in his balance or ambulation. No further exam was performed other than noting. His mentation is excellent.

IMPRESSION: Glioblastoma in the right occipital area. The patient is post primary therapy with temozolomide and external beam radiation therapy. He had recurrence in the surgical bed roughly four months later that was treated with radiosurgery. He was then started on Optune therapy and has been stable, if not improved in his imaging since that time. He has no current concerns or problems.

CHRISTENSON, DAVID P
MRN: E000369357
ACCT: E34723117 REG CLI
DOB: 11/14/53
DEPT: E.DICT

ASCENSION NE WI ST. ELIZABETH HOSPITAL, APPLETON, WI
RADIATION ONCOLOGY

PATIENT NAME: CHRISTENSON, DAVID P REPORT NO: 0922-0008

PLAN: He will continue on Optune therapy indefinitely. There is no data on circumstance in which this can be discontinued. He will be doing some traveling to Europe in the near future and we will have a one week break from his Optune therapy. During that period, he will reinstitute upon return. I will plan on seeing him back in 3 months with an MRI of the brain plus contrast prior to that visit. All questions were answered today.

Greater than 15 minutes, greater than 50% being counseling and coordination of care.

JOB ID: 176857
cc:
Trans: R1

Rick D. Davis, MD
Radiation Oncology
St. Elizabeth Hospital Cancer Center

Electronically Signed: RICK D DAVIS MD 10/11/18 0839

FINAL ORIGINAL IN COMPUTER PATIENT RECORD

CHRISTENSON, DAVID P
MRN: E000369357
ACCT: E34723117 REG CLI
DOB: 11/14/53
DEPT: E.DICT

DEPARTMENT OF RADIOLOGY

	D.O.B	AGE	SEX	EXAM DATE
CHRISTENSON, DAVID P	11/14/1953	64	M	09/18/18

LOC: M.RAD
Pt Ph#: 920-203-5636
MR#: 0000343818
Ordered By: DAVIS MD, RICK D
ACCT# 003754608
Status: REG CLI

EXAM#	TYPE/EXAM	RESULT
002857789	MRI/HEAD W/WO CONTRAST	

RICK D DAVIS, MD

HEAD W/WO CONTRAST

COMPARISON: MRI brain study with and without contrast dated 6/18/2018

HISTORY: Three-month follow-up.

TECHNIQUE: MRI of the brain was performed before and after intravenous administration of 10 mL of MultiHance gadolinium contrast.

FINDINGS:
BRAIN AND CSF SPACES: Postoperative findings of right craniotomy for tumor resection. Unchanged heterogeneous enhancement involving the right parietal occipital resection cavity extending to the right occipital and peritrigonal white matter. Unchanged FLAIR hyperintense signal surrounding the resection cavity and extending throughout the posterior right frontal, parietal, occipital and temporal lobes extension as well as extension into the external and internal capsules. FLAIR hyperintense signal extends across the right splenium of the corpus callosum. Unchanged FLAIR hyperintense signal in the left periventricular white matter scattered small foci of FLAIR hyperintense signal scattered throughout the white matter both cerebral hemispheres. Unchanged effacement of the right lateral ventricle. Slightly decreased effacement of the third ventricle with midline shift to the left of 4 mm. Susceptibility weighted images demonstrate hemosiderin staining associated with the resection cavity with scattered small foci in the right parietal lobe. Unchanged diffusion abnormality associated with the FLAIR hyperintense signal in the right splenium.
PITUITARY: Normal.
PINEAL: Normal.
VASCULATURE: Normal.
ORBITS: Normal.
NASAL CAVITY AND NASOPHARYNX: Normal.
PARANASAL SINUSES: There is patchy mucosal thickening of the ethmoid sinuses.
OTOMASTOID FINDINGS: Mastoid air cells are clear.
SKULL AND C-SPINE: Normal.

IMPRESSION:

DEPARTMENT OF RADIOLOGY

CHRISTENSON, DAVID P

D.O.B	AGE	SEX	EXAM DATE
11/14/1953	64	M	09/18/18

LOC: M.RAD
Pt Ph#: 920-203-5636
MR#: 0000343818
ACCT# 003754608
Status: REG CLI

Ordered By: DAVIS MD, RICK D

EXAM#	TYPE/EXAM	RESULT
002857789	MRI/HEAD W/WO CONTRAST	

1. Stable postoperative findings of right craniotomy for right occipital tumor resection with unchanged appearance of the heterogeneously enhancing resection cavity. No evidence of tumor progression.

2. FLAIR hyperintense signal surrounding the resection cavity and extending throughout the right cerebral hemisphere as detailed above. Unchanged mass effect with 4 mm midline shift to the left.

Lisa D. Roller, MD
Division of Neuroradiology
Radiology Associates of the Fox Valley, S.C.

RAFVCC
I.2

Electronically Signed By: Lisa Roller, MD
Signed Date/Time: 9/19/2018 8:11 AM

** REPORT SIGNED IN OTHER VENDOR SYSTEM 09/19/2018 **
Reported By: ROLLER, LISA MD

CC: DAVIS MD, RICK D

Edited Date: 09/19/18 by PROVIDER
Printed Date/Time: 10/29/2018 (1241)

ATTACHMENT D

TO THE RECONSIDERATION REQUEST

CGS
Jurisdiction B
P.O. BOX 20007
Nashville, TN 37202

MEDICARE DME

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

March 11, 2019

7-7-19

NOVOCURE INC
195 COMMERCE WAY
PORTSMOUTH NH 03801

Beneficiary Name: David Christenson
Medicare ID: XXXXXXXQP33
Appeal Number. 19053000193
Date(s) of Service: November 3, 2018, December 3, 2018 and January 3, 2019
Claim Control Number (CCN): 18310809384000, 18338812665000 and 19007808841000
Type of Service: Tumor Treatment Field Therapy (TTFT)
Supplier: NOVOCURE INC

Dear NOVOCURE INC:

Please note that if you did not request this appeal, you are receiving this letter as a copy.

DECISION

This letter is to inform you of **an UNFAVORABLE** Medicare Appeal decision. Based on a new and independent review of the claims at issue, we find the ELECTRICAL STIMULATION DEVICE USED FOR CANCER TREATMENT, INCLUDES ALL ACCESSORIES, ANY TYPE (E0766) is not covered by Medicare. The beneficiary is not responsible for payment. If you disagree with this decision, you may appeal to the Qualified Independent Contractor (QIC), C2C Solutions, Inc., as explained in the Future Appeal Rights section of this letter.

SUMMARY OF FACTS

Claims were submitted for the ELECTRICAL STIMULATION DEVICE USED FOR CANCER TREATMENT, INCLUDES ALL ACCESSORIES, ANY TYPE (E0766) for dates of service November 3, 2018, December 3, 2018 and January 3, 2019. The claims were initially denied on November 12, 2018, because Medicare guidelines were not met. A redetermination request was received on February 22, 2019. The redetermination case included the following documentation: medical records, administrative records and order.

APPLICABLE MEDICARE GUIDELINES AND RULES

The Medicare coverage policies are set forth below for the item or service in question. These rules are available at www.cgsmedicare.com.

CGS
Jurisdiction B
P.O. BOX 20007
Nashville, TN 37202

MEDICARE DME

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

- CMS Medicare Coverage Database, Local Coverage Determination (LCD)-L34823-Tumor Treatment Field Therapy (TTFT)
- Social Security Act, Section 1879, Limitation on Liability

EXPLANATION OF THE DECISION

The CMS Medicare Coverage Database, Local Coverage Determination (LCD)-L34823-Tumor Treatment Field Therapy (TTFT) states that for any item to be covered by Medicare the items or services must: 1) be eligible for a defined Medicare benefit category, 2) be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member, and 3) meet all other applicable Medicare statutory and regulatory requirements. It is expected that the beneficiary's medical records will reflect the need for the care provided. The beneficiary's medical records include the physician's office records, hospital records, nursing home records, home health agency records, records from other healthcare professionals and test reports. This documentation must be available upon request. Our review finds the following criteria have not been met:

- Tumor treatment field therapy (E0766) or therapy supplies (A4555) are not covered by Medicare as the currently published studies in the medical literature do not clearly document the effectiveness of this device. (LCD L34823-Tumor Treatment Field Therapy (TTFT), Coverage Indications, Limitations, and/or Medical Necessity)

A review of the documentation submitted with the redetermination request has been completed. Due to the Medicare guidelines discussed above, a favorable decision cannot be made at this time.

WHO IS RESPONSIBLE FOR THE BILL

After determining that the item or service will not be covered by Medicare, we must determine who is financially liable for the denied item or service. When an item or service is denied under §1862(a)(1), §1862(a)(9), or §1879(g) of the Social Security Act (the Act), we must determine if the beneficiary and the provider or supplier either knew or could reasonably be expected to know that the item or service would not be covered. This is known as the limitation on liability provision of §1879 of the Act.

If the beneficiary was informed by their provider or supplier in writing in advance of receiving the item/service that Medicare may not make payment (through receipt of an Advance Beneficiary Notice of Noncoverage (ABN)), the beneficiary may be responsible for the cost of the denied item or service. If the provider or supplier knew or could reasonably be expected to know the item or service would not be covered, but the beneficiary did not have such knowledge, then the provider or supplier may be responsible for the cost of the denied item or service.

In addition, we have determined that the supplier either knew or could reasonably be expected to know that the service/item would not be covered. After reviewing the claims, we have determined that the services were not reasonable and necessary. We have also determined the beneficiary could not have been expected to know these services were non-covered. Prior to furnishing this service you did not obtain a valid signed Advance Beneficiary Notice of Noncoverage notifying the beneficiary that Medicare may not pay. Based on the information contained in the CMS Medicare Coverage Database, Local Coverage Determination (LCD)-L34823-Tumor Treatment

CGS
Jurisdiction B
P.O. BOX 20007
Nashville, TN 37202

MEDICARE DME

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

Field Therapy (TTFT), you could have been expected to know these services were non-covered. Therefore, you are liable for full charges for the services.

You may not bill the beneficiary for the cost of the denied item or service, and must refund any monies collected from the beneficiary.

Beneficiaries who have incurred a charge for this service may be due a refund. In order to receive reimbursement, the beneficiary must submit the following to this office: (1) a copy of this notice, (2) the supplier's invoice, and (3) a receipt or other documents indicating the beneficiary has made payment.

FUTURE APPEAL RIGHTS

If you disagree with this decision, you must request a reconsideration, in writing, within 180 days of receiving this letter. Your reconsideration request must include a copy of this letter along with the beneficiary's name, Medicare number, item or service in question, date of service, name of person appealing, signature, and date of signature. You may request an appeal by using the form enclosed with this letter. A copy of the reconsideration request form is also located at http://www.cgsmedicare.com/jb/index.html or at www.C2Cinc.com. Reconsideration requests must be mailed to:

C2C Solutions, Inc.
Attn: DME Qualified Independent Contractor (QIC)
P. O. Box 44013
Jacksonville, FL 32231-4013

All evidence should be submitted with the reconsideration request. As explained in the Explanation of Decision section above, your reconsideration request should include documentation that shows the tumor treatment field therapy (E0766) is covered by Medicare and records that show the currently published studies in the medical literature does document the effectiveness of this device. All evidence must be presented before the reconsideration decision is issued. You will not be allowed to submit any new evidence to the Administrative Law Judge or the Medicare Appeals Council unless you can demonstrate good cause for not submitting the evidence to the QIC during the reconsideration process.

NOTE: You do not need to resubmit documentation that was submitted as part of the redetermination. This information will be forwarded to the QIC as part of the case file utilized in the reconsideration process.

If you need more information or have any questions, please visit our Web site at http://www.cgsmedicare.com/jb/index.html or call 1-866-590-6727.

Sincerely,

CGS, DME MAC Jurisdiction B
Medicare Appeals Department

cc: David Christenson

19053000193 6723630001

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C2C INNOVATIVE SOLUTIONS, INC.
PO BOX 44013
JACKSONVILLE FL 32231-4013

USPS TRACKING #

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Redetermination Case File Request/Transmittal
DME QIC Form

COMPLETED BY QIC

1. Joint File Request Type	**X QIC Request**	**Misfiled**	**Misrouted**
☐ **Supplemental File Request/Basis for Request**			
2. QIC Reconsideration #	**1-8486340738**	**Reconsideration Request Date**	April 22, 2019
3. AC Name / Number	**CGS Administrators(17013)**		
4. Claim Type	☐ **Part B** ☒ **DME**	**Redetermination #**	**Multiple**
4a. Overpayments	☐ **RAC** ☐ **AC/MAC MR Probe**	☐ **PSC/ZPIC** ☐ **Overpayment-other**	

5. * Beneficiary Name	**Bene HIC#**	**Provider #**	**Redet. Date**	**DOS**
Multiple	**Multiple**		**Multiple**	**Multiple**
Claim # or CPT/HCPCS Codes at issue:	**Multiple**			

* Use Redetermination Request Continuation Sheet for multiple beneficiaries

COMPLETED BY AC

AC Acknowledgement: Return to Name and QIC Fax #	**Candace Diehl**
AC Receipt Date & Signature	

Exhibits List: Label exhibits with the letters provided below, and place them in order by letter. Refer to Exhibit List Quick Guide in JOA for detailed description of exhibits.

Procedural Documents	☐ A. Claims and System Screens ☒ B. MSN or RA ☒ C. Redetermination Request	☒ D. Redetermination Notice ☐ E. Appointment of Rep. ☐ F. Other
Evidentiary Documents	☒ G. Medical Records ☐ H. Referral to/from Contractor Med. Staff ☐ I. Contractor Medical Policies ☐ L. Other	☒ J. Regs/CMS Rulings/NCDs, etc. ☐ K. Overpayment Extrapolation Materials

Comments (discrepancies, no redetermination, other comments):
☐ No redetermination ☐ Claim fully paid ☐ Incorrect HICN ☐ Other _____
☐ Complete case previously sent to _________ (QIC) on (date) . No additional appellant information.
☐ **RAC** ☐ **PSC/ZPIC**_☐ **AC/MAC MR Probe** ☐ **Overpayment** ☐ **CERT**

Interest in ALJ Participation: ☐ Yes ☐ No
Position Paper Enclosed: ☐ Yes ☐ No

Form Completed By			
Name of Contact Person		**Contact Phone #**	
Date Sent		**# of Boxes**	
QIC Acknowledgement – AC Fax #			
QIC Receipt Date & Signature			

Redetermination Request Section 5

QIC Recon #	Beneficiary Name / HIC	Claim #	CPT/HCPCS	Dates of Service	Redeter Date	AC Redeter #
1-8486340738	David Christenson 340483639A	18310809384000	E0766	11/03/2018	03/11/19	19053000193
1-8486340738	David Christenson 340483639A	18338812665000	E0766	12/03/2018	03/11/19	19053000193
1-8486340738	David Christenson 340483639A	19007808841000	E0766	01/03/2019	03/11/19	19053000193

A

CLAIM FORMS

B

MSN/RA
(if applicable)

Change Healthcare	EFT/Check #: 09183160041	EFT/Check Date: 11/12/2018	EFT/Check Amount: $ .00	Payment Type: NON
	Payer Name: CGS - DME MAC JURISDICTION B		CH Payer Id: MR031	CH Process Date: 11/13/2018
	Provider Name: NOVOCURE INC	Tax Id: 205063536	NPI: 1255617569	Other Payee Id:
ERA Check 1 of 1	Address: 195 COMMERCE WAY, PORTSMOUTH NH 038019999		Addl. Payee Id: 1255617569	Total PLB Adj Amt: 21000

Service Dates: 11/03/2018	Processing Status: 4 - Denied		
Payer Claim # / Medicare ICN #: 18310809384000	CH Claim Trace Id: 309334771250657	Place Of Service:	Total Adjustment Amount: $ .00
Charge: $ 21,000.00	Paid: $ .00	Patient Responsibility: $ -	Deductible: $ -
Co-Insurance: $ -	Co-Pay: $ -	Other/Crossover Insurance:	

Remark Codes:	N793	Alert: CMS is changing from the Medicare Health Insurance Claim number (HICN) to the new Medicare Beneficiary Identifier (MBI). You can use either the HICN or MBI during the transition period. Visit www.cms.gov/newcard for important dates and information about this change. Start: 07/01/2017 | Last Modified: 11/01/2017 Notes: (Modified 11/1/2017)
	MA13	Alert: You may be subject to penalties if you bill the patient for amounts not reported with the PR (patient responsibility) group code. Start: 01/01/1997 | Last Modified: 04/01/2007 Notes: (Modified 4/1/07)
	MA01	Alert: If you do not agree with what we approved for these services, you may appeal our decision. To make sure that we are fair to you, we require another individual that did not process your initial claim to conduct the appeal. However, in order to be eligible for an appeal, you must write to us within 120 days of the date you received this notice, unless you have a good reason for being late. Start: 01/01/1997 | Last Modified: 04/01/2007 Notes: (Modified 10/31/02, 6/30/03, 8/1/05, 4/1/07)
	M25	The information furnished does not substantiate the need for this level of service. If you believe the service should have been fully covered as billed, or if you did not know and could not reasonably have been expected to know that we would not pay for this level of service, or if you notified the patient in writing in advance that we would not pay for this level of service and he/she agreed in writing to pay, ask us to review your claim within 120 days of the date of this notice. If you do not request an appeal, we will, upon application from the patient, reimburse him/her for the amount you have collected from him/her in excess of any deductible and coinsurance amounts. We will recover the reimbursement from you as an overpayment. Start: 01/01/1997 | Last Modified: 11/01/2010 Notes: (Modified 10/1/02, 6/30/03, 8/1/05, 11/5/07, 11/1/10)
	N115	This decision was based on a Local Coverage Determination (LCD). An LCD provides a guide to assist in determining whether a particular item or service is covered. A copy of this policy is available at www.cms.gov/mcd, or if you do not have web access, you may contact the contractor to request a copy of the LCD. Start: 05/30/2002 | Last Modified: 07/01/2010 Notes: (Modified 4/1/04, 7/1/10)

PATIENT - SUBSCRIBER INFORMATION

Patient Name: CHRISTENSON, DAVID	Patient Id: 7QR9QM0QP33	Patient Control Number: 0001013346
Corrected Patient/Subscriber Name:		Corrected Patient/Subscriber Member ID:
Subscriber Name:	Subscriber Id:	Group/Policy Id:
Other Subscr. Name:	Other Subscriber Id:	Group/Policy Id:

REMITTANCE PROCESSING INFORMATION - SERVICE LINE DETAIL

Svc Line #	Service Date	Proc Code - Units / Modifiers	Charge $	Allowed $	Not Allowed $	Deductible $	Co-Ins $	Co-Pay $	Late Filing Red. $	Paid $
1	11/03/2018	E0766 - 0 / KF, RR	21,000.00	.00	.00	-	-	-	-	-

SUPPLEMENTAL INFORMATION/ADJUSTMENT INFORMATION - SERVICE LINES

Svc Line #	Core Business Scenario	Supp/Adj Group Code	Description	Supp/Adj Reason Code	Description	Amount $
1	3	CO	Contractual Obligations	50	These are non-covered services because this is not deemed a 'medical necessity' by the payer. Usage: Refer to the 835 Healthcare Policy Identification Segment (loop 2110 Service Payment Information REF), if present. Start: 01/01/1995 | Last Modified: 07/01/2017	21,000.00

Claim 1 of 1	Page 1 of 1

Change Healthcare

ERA Check 1 of 1

EFT/Check #: 09183440058	EFT/Check Date: 12/10/2018	EFT/Check Amount: $ .00	Payment Type: NON
Payer Name: CGS - DME MAC JURISDICTION B		CH Payer Id: MR031	CH Process Date: 12/11/2018
Provider Name: NOVOCURE INC	Tax Id: 205063536	NPI: 1255617569	Other Payee Id:
Address: 195 COMMERCE WAY, PORTSMOUTH NH 038019999		Addl. Payee Id: 1255617569	Total PLB Adj Amt: 21000

Service Dates: 12/03/2018	Processing Status: 4 - Denied		
Payer Claim # / Medicare ICN #: 18338812665000	CH Claim Trace Id: 337347979056658	Place Of Service:	Total Adjustment Amount: $ .00
Charge: $ 21,000.00	Paid: $ .00	Patient Responsibility: $ -	Deductible: $ -
Co-Insurance: $ -	Co-Pay: $ -	Other/Crossover Insurance:	

Remark Codes:		
	N793	Alert: CMS is changing from the Medicare Health Insurance Claim number (HICN) to the new Medicare Beneficiary Identifier (MBI). You can use either the HICN or MBI during the transition period. Visit www.cms.gov/newcard for important dates and information about this change. Start: 07/01/2017 | Last Modified: 11/01/2017 Notes: (Modified 11/1/2017)
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	M25	The information furnished does not substantiate the need for this level of service. If you believe the service should have been fully covered as billed, or if you did not know and could not reasonably have been expected to know that we would not pay for this level of service, or if you notified the patient in writing in advance that we would not pay for this level of service and he/she agreed in writing to pay, ask us to review your claim within 120 days of the date of this notice. If you do not request an appeal, we will, upon application from the patient, reimburse him/her for the amount you have collected from him/her in excess of any deductible and coinsurance amounts. We will recover the reimbursement from you as an overpayment. Start: 01/01/1997 | Last Modified: 11/01/2010 Notes: (Modified 10/1/02, 6/30/03, 8/1/05, 11/5/07, 11/1/10)
	N115	This decision was based on a Local Coverage Determination (LCD). An LCD provides a guide to assist in determining whether a particular item or service is covered. A copy of this policy is available at www.cms.gov/mcd, or if you do not have web access, you may contact the contractor to request a copy of the LCD. Start: 05/30/2002 | Last Modified: 07/01/2010 Notes: (Modified 4/1/04, 7/1/10)

PATIENT - SUBSCRIBER INFORMATION

Patient Name: CHRISTENSON, DAVID	Patient Id: 7QR9QM0QP33	Patient Control Number: 0001013346
Corrected Patient/Subscriber Name:		Corrected Patient/Subscriber Member ID:
Subscriber Name:	Subscriber Id:	Group/Policy Id:
Other Subscr. Name:	Other Subscriber Id:	Group/Policy Id:

REMITTANCE PROCESSING INFORMATION - SERVICE LINE DETAIL

Svc Line #	Service Date	Proc Code - Units / Modifiers	Charge $	Allowed $	Not Allowed $	Deductible $	Co-Ins $	Co-Pay $	Late Filing Red. $	Paid $
1	12/03/2018	E0766 - 0 / KF, RR	21,000.00	.00	.00	-	-	-	-	-

SUPPLEMENTAL INFORMATION/ADJUSTMENT INFORMATION - SERVICE LINES

Svc Line #	Core Business Scenario	Supp/Adj Group Code	Description	Supp/Adj Reason Code	Description	Amount $
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Claim 1 of 1	Page 1 of 1

Change Healthcare

ERA Check 1 of 1

EFT/Check #: 09190110009	EFT/Check Date: 01/11/2019	EFT/Check Amount: $ .00	Payment Type: NON
Payer Name: CGS - DME MAC JURISDICTION B		CH Payer Id: MR031	CH Process Date: 01/14/2019
Provider Name: NOVOCURE INC	Tax Id. 205063536	NPI: 1255617569	Other Payee Id:
Address: 195 COMMERCE WAY, PORTSMOUTH NH 038019999		Addl. Payee Id: 1255617569	Total PLB Adj Amt: 21000

Service Dates: 01/03/2019	Processing Status: 4 - Denied		
Payer Claim # / Medicare ICN #: 19007808841000	CH Claim Trace Id: 004362849314658	Place Of Service:	Total Adjustment Amount: $ .00
Charge: $ 21,000.00	Paid: $ .00	Patient Responsibility: $ -	Deductible: $ -
Co-Insurance: $ -	Co-Pay: $ -	Other/Crossover Insurance:	

Remark Codes:		
	N793	Alert: CMS is changing from the Medicare Health Insurance Claim number (HICN) to the new Medicare Beneficiary Identifier (MBI). You can use either the HICN or MBI during the transition period. Visit www.cms.gov/newcard for important dates and information about this change. Start: 07/01/2017 | Last Modified: 11/01/2017 Notes: (Modified 11/1/2017)
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	M25	The information furnished does not substantiate the need for this level of service. If you believe the service should have been fully covered as billed, or if you did not know and could not reasonably have been expected to know that we would not pay for this level of service, or if you notified the patient in writing in advance that we would not pay for this level of service and he/she agreed in writing to pay, ask us to review your claim within 120 days of the date of this notice. If you do not request an appeal, we will, upon application from the patient, reimburse him/her for the amount you have collected from him/her in excess of any deductible and coinsurance amounts. We will recover the reimbursement from you as an overpayment. Start: 01/01/1997 | Last Modified: 11/01/2010 Notes: (Modified 10/1/02, 6/30/03, 8/1/05, 11/5/07, 11/1/10)
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Corrected Patient/Subscriber Name:		Corrected Patient/Subscriber Member ID:
Subscriber Name:	Subscriber Id:	Group/Policy Id:
Other Subscr. Name:	Other Subscriber Id:	Group/Policy Id:

REMITTANCE PROCESSING INFORMATION - SERVICE LINE DETAIL

Svc Line #	Service Date	Proc Code - Units / Modifiers	Charge $	Allowed $	Not Allowed $	Deductible $	Co-Ins $	Co-Pay $	Late Filing Red. $	Paid $
1	01/03/2019	E0766 - 0 / KF, RR	21,000.00	.00	.00	-	-	-	-	-

SUPPLEMENTAL INFORMATION/ADJUSTMENT INFORMATION - SERVICE LINES

Svc Line #	Core Business Scenario	Supp/Adj Group Code	Description	Supp/Adj Reason Code	Description	Amount $
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Claim 1 of 1	Page 1 of 1

C

AC REDETERMINATION REQUEST

MEDICARE DME Redetermination Request Form

Supplier Information

Supplier Name Novocure INC

PTAN 6723630001 NPI 1255617569

Tax ID 205063536

Address 195 Commerce Way

City Portsmouth

State NH Zip Code 03801

Phone Number (603) 617-4768

___ Jurisdiction A - Noridian Healthcare Solutions
X Jurisdiction B - CGS
___ Jurisdiction C - CGS
___ Jurisdiction D - Noridian Healthcare Solutions

Beneficiary Information

Patient Name David Christenson

Medicare Number 7QR9QM0QP33

State Wisconsin

Phone Number (920)203-5636

Requestor's Name/Supplier Contact Name Todd Glynn

Requestor's Signature (required) Todd Glynn Date 2-21-2019

Overpayment Appeal _ Yes If yes, who requested overpayment: _ Medical Review _ ZPIC/PSC _ CERT _ Recovery Auditor

Date of Service	HCPCS & Modifiers	CCN	Date of Initial Determination
11/03/2018	E0766 KF RR	18310809384000	11/12/2018
12/03/2018	E0766 KF RR	18338812665000	12/10/2018
01/03/2019	E0766 KF RR	19007808841000	01/11/2019

Suggested Documentation Check List: X Medicare Remittance Advice ___ ABN X CMN/DIF/Physician's Written Order X Medical Documentation

Reasons/Rationale - The submission of this redetermination is in regards to the denial code received: (CO-50)-"These are non-covered services because this is not deemed a 'medical necessity' by the payer." Novocure has been FDA approved since April 2011. Please see attached documentation for review.

Fax Numbers

Noridian Healthcare Solutions - JA 1-701-277-7855
CGS Administrators, LLC - JB 1-615-660-5976
CGS Administrators, LLC - JC 1-615-782-4630
Noridian Healthcare Solutions - JD 1-701-277-7886

CMS CENTERS FOR MEDICARE & MEDICAID SERVICES

April 12, 2016.

D

AC REDETERMINATION NOTICE

E

APPOINTMENT OF REPRESENTATIVE

F

PSC, RAC, Overpayment

G

MEDICAL/ Administrative RECORDS

novocure

Invoice

Novocure Inc.
195 Commerce Way
Portsmouth, NH 03801

DATE: NOVEMBER 03, 2018
INVOICE # [110]

Bill To:
David Christenson
5754 Clevedon Lane
OshKosh, WI 54904

Ship To:
David Christenson
5754 Clevedon Lane
OshKosh, WI 54904

Ordered By: Rick Davis, MD

ITEM #	DESCRIPTION	QTY	UNIT PRICE	LINE TOTAL
TFH9000	NOVO-TTF 100A PLUS TRANSDUCERS	1	$21,000	$21,000
			SUBTOTAL	$21,000
			SALES TAX	0
			TOTAL	**$21,000 Per Month**

PLEASE REMIT TO: Novocure Inc., 195 Commerce Way, Portsmouth, NH 03801
Make all checks payable to Novocure Inc.

If you have any questions concerning this invoice, contact Justin Kelly, RN @ 603-501-4299.

novocure

Invoice

Novocure Inc.
195 Commerce Way
Portsmouth, NH 03801

DATE: DECEMBER 03, 2018
INVOICE # [111]

Bill To:
David Christenson
5754 Clevedon Lane
OshKosh, WI 54904

Ship To:
David Christenson
5754 Clevedon Lane
OshKosh, WI 54904

Ordered By: Rick Davis, MD

ITEM #	DESCRIPTION	QTY	UNIT PRICE	LINE TOTAL
TFH9000	NOVO-TTF 100A PLUS TRANSDUCERS	1	$21,000	$21,000
			SUBTOTAL	$21,000
			SALES TAX	0
			TOTAL	$21,000 Per Month

PLEASE REMIT TO: Novocure Inc., 195 Commerce Way, Portsmouth, NH 03801
Make all checks payable to Novocure Inc.

If you have any questions concerning this invoice, contact Justin Kelly, RN @ 603-501-4299.

novocure

Invoice

Novocure Inc.
195 Commerce Way
Portsmouth, NH 03801

DATE: JANUARY 03, 2019
INVOICE # [112]

Bill To:
David Christenson
5754 Clevedon Lane
OshKosh, WI 54904

Ship To:
David Christenson
5754 Clevedon Lane
OshKosh, WI 54904

Ordered By: Rick Davis, MD

ITEM #	DESCRIPTION	QTY	UNIT PRICE	LINE TOTAL
TFH9000	NOVO-TTF 100A PLUS TRANSDUCERS	1	$21,000	$21,000
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Make all checks payable to Novocure Inc.

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David P. Christenson
5754 Clevedon Lane
Oshkosh, WI 54904

October 11, 2018

Attn: Medicare Appeals
Re: Denial of My Cancer Treatment
Policy#: 340483639A

To whom it may concern:

This letter is in response to Medicare denial of my physician's prior authorization request for coverage of Tumor Treatment Fields therapy (TTF) using Optune for my recurrent glioblastoma.

I am submitting this letter as an urgent member grievance so that I may obtain approval of my badly needed, FDA APPROVED, treatment for my cancer.

According to the letter we received from Medicare, the request for coverage for services was denied based upon the following reason: "Experimental".

First of all, I have to strongly disagree with this rationale. This treatment has been approved by the **United States Food and Drug Administration** for treatment of glioblastoma. Furthermore, my physician feels that this treatment is my best hope for slowing down the progression of my disease. I find it unconscionable that Medicare is second guessing the treatment decisions of my physician, Dr. Rick Davis, who is one of the country's leading experts on this treatment.

TTF is my **best option** to treat this fatal disease. I have submitted the attached clinical information from my physicians as well as peer reviewed literature to assist you in considering approval of this treatment.

This procedure has been covered by many local and national insurance companies including: Humana Medicare Advantage, AARP Medicare Advantage and Aetna Medicare Advantage, This is only a representative sampling of payers covering Optune for this cancer indicating that there is enough "proven" evidence to warrant coverage for Optune in treating glioblastoma. **I am demanding that my clinical situation be reviewed by a board certified physician specializing in neuro-oncology or neurosurgery who has specific expertise in treating patients with glioblastoma with TTF.**

I am a 65 year old gentleman being treated for glioblastoma. I have been married for 41 years. I have two children, 36 and 33 years old, and two grandchildren ages 6 and 3. I am currently not working (retired). I did work part-time prior to my disease. I worked in the information technology field doing software development for 30+ years. After retirement, I worked part-time driving for a company whose clients were primarily veterans. I transported veterans to their medical appointments. I retired after 25 years for one company. I subsequently worked 6 years for the transportation company. In my free time, I enjoy biking, golfing, traveling and listening to audio books.

Initially, I had experienced headaches for several weeks. When they worsened and included vomiting, I went to urgent care and then to the hospital emergency room. I had emergency surgery the following day. I was on chemotherapy and radiation for 6 weeks after surgery. Subsequently, I was on a chemotherapy regimen of 5 days a week for one year. I experienced profound fatigue during and for some time after the chemotherapy and radiation treatment phases. I currently experience some fatigue, but to a much lesser degree. With Optune I have virtually no side effects aside from mild fatigue.

After discussing treatment options with Dr. Rick Davis, my doctor decided to prescribe Optune. Given the aggressive nature, and extremely limited treatment options of my disease, my doctor recommended I receive coverage for Optune, as it is the best FDA approved option at this time for treating my recurrent glioblastoma. I began utilizing TTFields on 10/03/2016.

I believe Optune is preventing the development of new tumor cells, which I understand is its purpose. I am currently 3 years beyond my GBM diagnosis and I am considered to be a long-term survivor. I attribute this to Optune. My initial prognosis was extremely grim. Optune has provided a non-invasive treatment that allows me to live a fairly normal life. At the same time, my MRI results have consistently indicated that this treatment is working, giving my family and me reason to be optimistic and hopeful for the future.

Please note that the NCCN Guidelines (National Comprehensive Cancer Network) were updated for 2015 to include TTFields treatment for recurrent glioblastoma as a category 2B recommendation.

I am aware that my cancer is considered an "orphan disease," due to the rarity of people who get glioblastoma. Despite these interventions I have received to date, TTF therapy is my best hope to control my brain tumor.

I cannot emphasize enough the urgency and importance of this matter.

Should you have any additional questions regarding my condition or the proposed treatment, please feel free to contact me at (920)-203-5636.

I also give consent for Novocure to work on the appeal on my behalf.

Thank you for your timely consideration and hopeful approval of this case.

Sincerely,

David P Christenson

David P. Christenson

Attachments

OPTUNE

Optune® Prescription Form

Please fax or email signed and completed forms with medical records, face sheet, and copies of insurance card(s) to 603-501-4298 or support@novocure.com

I. PRESCRIPTION INFORMATION

Patient Name: David Christenson (required)

Date of Birth: 11/14/1953 (required)

Please check the appropriate box:

☐ New Patient order

☒ Renewal

Is this patient enrolling in an Investigator Sponsored Trial (IST) or Cooperative Group Trial (e.g. RTOG)? ☐ Yes If yes, which trial? ______

Optune is comprised of: an Electric Field Generator (the "Device"), Transducer Arrays (the "Arrays"), power supply items, and accessories.

ICD-10 Code: C71 . 9 (required) Diagnosis Description: Recurrent GBM

I prescribe use of Optune, as described above, for a period of: (check box required)

☐ 3 months

☒ 6 months

Davis, Rick, D
Prescriber Name (Last, First, Middle Initial): (required)

Same
Name of Preferred Office Contact

NPI: 1861460974 (required)

920 738 2184
Phone

920 236 1605
Phone

920 236 1628
Fax

rick.davis2@ascension.org
Email

By signing and dating, I attest that I am prescribing Optune (DO NOT SUBSTITUTE) as medically necessary. I have read and understand all safety information and other instructions for use included with Optune.

(required) Rick Davis MD (required) 10-29-2018

II. ORDER INFORMATION

Treatment education, head preparation and array application will take place in the patient's home. Upon completion of the education session, the patient or caregiver may initiate treatment in the presence of Novocure personnel.

Preferred Treatment Start date (MM/DD/YYYY): ______

Please allow **5 business days** from submission of all required paperwork and preferred treatment start date.

Notes

OPTUNE

Optune™ Prescription Form

Fax the completed form with signature to 603-501-4298; or Email to Support@novocure.com

III. PATIENT INFORMATION (PLEASE COMPLETE IN FULL)

Patient Information

Permanent Address: 5754 CLEVEDON LANE

City: OSHKOSH **State:** WI **Zip:** 54904 **Phone:** (920) 203-5636

Family Contact: BARBARA CHRISTENSON **Phone:** (920) 203-5637

[✓] **Shipping and mailing address same as permanent address.**

[ ] **Use the address below for shipping and mailing purposes related to equipment, supplies and billing.** Patient must reside at this address:

Shipping and Mailing Address: ____________________

City: ______ **State:** ______ **Zip:** ______ **Phone:** ______

Insurance Information

Primary Insurance: NETWORK HEALTH

Patient ID#: 10541902 **Insurance Phone Number:** (920) 720-1300

Group#: 101291 **Group Name:** STATE OF WISCONSIN

Primary Insured (Subscriber) Name: BARBARA J. CHRISTENSON

Relationship to Patient: WIFE **Subscriber Date of Birth:** 11-17-53

****If you have secondary insurance, please attach this information if applicable.**

The use of "I" or "you" in this document refers to the patient named in the "Signatures" block.

Authorization to Release Records to Novocure

I authorize my physician and the practice, facility and hospital of my physician and any other holder of medical information about conditions for which I am being treated to release to Novocure Inc. and affiliated companies (together "Novocure") any information necessary for treatment, payment and healthcare operations related to my use of Optune. I authorize Novocure employees to deliver equipment and provide education in my home as well as attend my appointments as necessary to provide technical assistance to my physician and healthcare practitioners. I also authorize Novocure, my physician and the practice, facility and hospital of my physician and any other holder of medical information about conditions for which I am being treated to release such information to my insurer. These authorizations apply to my current physician and previous physicians. I understand that Novocure may and likely will use the information to seek a determination of whether my insurer will cover my use Optune.

Authorization To Discuss Care

I authorize Novocure to discuss my care with the family members and/or caregivers listed below. I may revoke this authorization at any time by calling or emailing Novocure at 855-281-9301 or support@novocure.com.

List all authorized individuals: BARBARA CHRISTENSON

Signatures: David Christenson

Patient Name (please print): DAVID P. CHRISTENSON Date: 9/22/16

If anyone other than patient completes or signs this form, please enter the following information:

Name: ______ Telephone Number: ______

Address: ______ City: ______

State: ______ Zip ______

Relationship to Patient: ______ Reason for Signing: ______

this week

ASSESSMENT of NEED

Customer Name:	David Christenson	**Date:**	9/27/16
Customer #	1013346		
DSS/Site	Nancy Newberg / St. Elizabeth Cancer Center	**Initiation:**	Home ☑ Office ☐

Responsible Party/ Emergency Contact:	Barbara (wife)	**Tel:**	920-203-5636

Patient acknowledges that financial responsibility has been discussed and agreed to: *(Indicate date of welcome call and person spoken to)*
Judi 9/27/16

How did you hear about Optune Therapy? radiation oncologist

What factors led to the decision to start treatment?

Did you receive a package from us containing printed material and DVD? Yes No **Not Sure**

Does patient live alone? Yes No | Patient has access to telephone: **Yes** No

Is patient residence? **Home** Assisted Living Other facility:

In what type of structure do you reside? **House** - Apart/Condo- Assisting Living - Rehab Facility

Where will parking be? **Yes** No driveway

How will we enter / exit residence? FRont door

Should I be made aware of any safety concerns? ex lack of lighting , no elevator (if apt is not on 1st floor)
Please specify: N/A

Are there any pets in your home? Yes **No**	Cats #	Dogs #	Other types #

Can pets be placed in another room while DSS present? Yes No **N/A**

Is there smoking in the home? Yes **No**

Is there anything that our DSS should know about the home environment or the people residing there that could be important for the safety of the visit? N/A

Is patient able to speak: **Yes** No If yes, what is his/her primary language? English

Does patient have adequate electrical capacity to utilize device and recharge batteries **Yes** No

Does he/she require assistance with mobility? Yes **No** on his own

Are you employed? Yes **No** If so do you plan on continuing to work? Yes **No**

If you are planning on continuing to work what is your occupation? Retired

Have you discussed treatment during work hours with your employer? Yes **No**

See Technical Review Checklist: Yes - No

Other: (Explain)

Explain any special needs or additional training required (if applicable) N/A ☐

Training on the Optune device is performed, conducted, and observed by certified physicians in accordance with FDA approval guidelines.

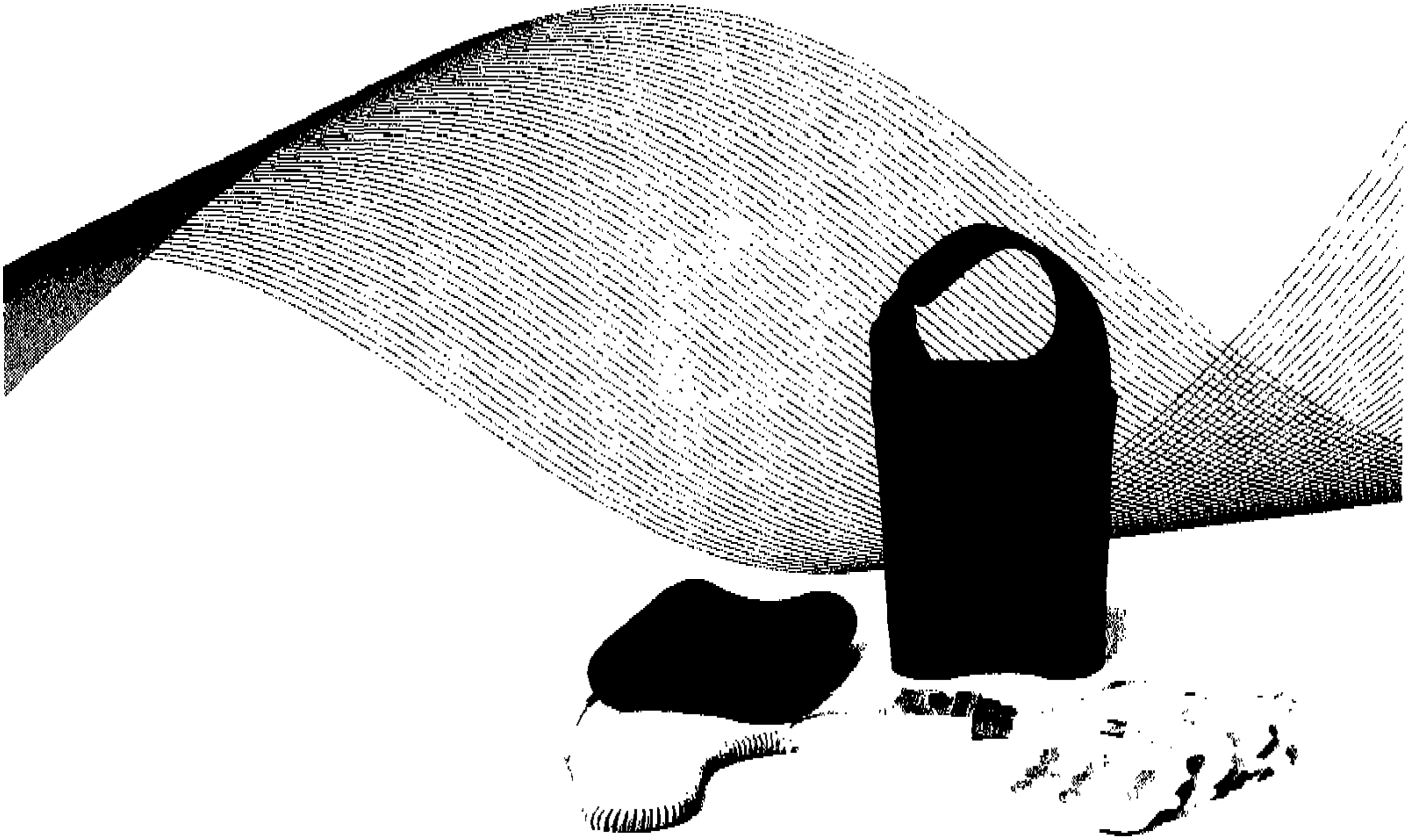
Completed by:	[signature]	**Date:**	9/27/16

QSF-DME-027 Rev. 02

Printed on: 24 May 2016, 11:01:11 am; Printed by: RSULLIVAN.

David Christenson

OPTUNE® | OPTUNE® SERVICE AGREEMENT



Supply Terms For Optune®

Background

Novocure™ Inc. is referred to as "we" or "Novocure" in this service agreement ("Service Agreement"). The use of "you" or "your" refers to the patient named in the associated Service Agreement. All capitalized terms not defined herein have the meaning defined in the Service Agreement.

Supply Terms

Optune (the "System") is comprised of two main components: (1) an Electric Field Generator (the "Device"); and (2) INE Transducer Arrays (the "Arrays") that are disposable supplies to the Device. The System also consists of power supply items and accessories.

Novocure's affiliates hold patents that cover the System, various components of the System, and using the System. Novocure hereby grants an expressly conditional license to you to use the inventions covered by those patents under the terms set forth herein. No other licenses to you are implied.

As an element of consideration for the grant of a license to you, you agree to pay Novocure a monthly fee for access to the System. Notwithstanding anything to the contrary contained in this agreement, any use of the System for which this element of consideration is absent is not licensed under the patents.

You acknowledge that, taken together, the consideration due to Novocure for access to the System reflects only the value of the "use" rights conferred by Novocure, and does not provide you with the same suite of rights that would accompany an unconditional sale. Notwithstanding anything to the contrary contained in this agreement, (1) you are not licensed to use the Device with Arrays that were not purchased from Novocure; and (2) you are not licensed to use any given Array for more than seven (7) days.

You understand that the Device shall at all times remain the property of Novocure.

You understand and agree that Novocure has the right to inspect the System upon request and that you may be responsible for the replacement value of the System in the event it is lost, damaged, or stolen while in your possession or control.

You understand that: (i) Novocure has the option to provide new or used equipment including the Device, power supplies and accessories; (ii) you shall not modify or alter any equipment provided to you by Novocure; (iii) you will notify Novocure immediately of any equipment problems; and (iv) the equipment is only to be used upon the order and direction of your doctor.

You agree to notify Novocure if you take a break from using the System for any period of two (2) weeks or longer. In the event that the duration of a break exceeds eight (8) weeks, you agree to return the Device to Novocure and you understand that Novocure will have the option of closing your account. Thereafter, if you desire to resume using the System, you may contact your doctor and Novocure, and Novocure will review your account and work with your doctor to re-start your use of the System. At that time, Novocure may provide you another System, and you understand that you would need to sign a new Service Agreement.

You understand that the System fees will continue until the date that you call Novocure to pick up the System. You understand that Novocure may stop providing the technical support for the System and may stop providing additional Arrays or replacement items if you fail to comply with the terms of the Service Agreement and Supply Terms, including failure to pay amounts owed or to remit payments due to Novocure that you receive directly from payors.

Patient Care Responsibilities

You understand and acknowledge that (1) your care is under the supervision and control of your treating physician or other health care provider (e.g., nurse practitioner, physician's assistant) who is appropriately licensed, trained and authorized to prescribe and administer the System, (2) your physician or other health care provider has prescribed the System as part of your treatment and has explained to you its risks, advantages, possible complications and alternatives, and why it is considered necessary treatment for your condition, (3) Novocure's services do not include diagnostic, prescriptive, or other functions pertaining to licensed physicians or health care providers, and (4) your physician or other health care provider is solely responsible for diagnosing and prescribing drugs, equipment, and therapy for your condition and otherwise supervising and controlling your medical condition.

Financial Responsibilities

The rental fee for the System, including use of the Device, related power supplies/accessories and Arrays for 30 days is $21,000.

Please call (855) 281-9301 if you have any questions about your financial responsibilities.

Novocure™ will review your insurance or third-party payor (together "Payor") coverage for the purposes of providing you with an estimate of your out-of-pocket costs associated with the rental fee to use the Device and the purchase of Arrays. Novocure will also prequalify you for eligibility for our Patient Assistance Programs. Formal qualification for financial assistance will require a separate application and documentation of income.

Novocure will submit a claim to your Payor for the System and may appeal such claim if denied. Novocure will bill you for your financial responsibilities related to the System when i) your Payor affirms coverage for your use of the System at the list rental fees and supply prices for the System or ii) Novocure elects not to continue appeals of your case.

If your cost share for the System is not affordable or your Payor refuses to provide coverage for the System, you can also apply to Novocure for financial assistance.

Please contact 855-281-9301 or email **support@novocure.com** to inquire about financial assistance programs.

Warranty Information

Novocure will provide a replacement Device in the event of malfunction that cannot be corrected over the phone by our technical support staff. Novocure will provide replacement Arrays in the event that the Transducer Arrays are defective according to manufacturer standards. Novocure will provide replacement power supplies and accessories in accordance with the expected useful lifetime of these items. The above warranty is only valid if the System is used in accordance with the User Manual provided to you. This warranty is personal to you and non-transferable.

Lost equipment, including the Device, Arrays, power supplies and related accessories, and equipment damaged by you or your caregivers is not covered by this warranty.

Patient Information Form For Optune®

Background

Novocure™ Inc. is referred to as "Novocure" in this service agreement ("Service Agreement"). The use of "you" or "your" refers to the patient named in the associated Service Agreement. All capitalized terms not defined herein have the meaning defined in the Service Agreement.

Notice of Privacy Practices

THIS NOTICE DESCRIBES HOW HEALTH INFORMATION ABOUT YOU MAY BE USED AND DISCLOSED AND HOW YOU CAN GET ACCESS TO THIS INFORMATION. PLEASE REVIEW IT CAREFULLY.

Please contact 855-281-9301 or **support@novocure.com** if you have questions.

Purpose of This Notice

This notice will tell you about the ways in which Novocure may use and disclose your health information that identifies you ("PHI"). We also describe your rights and certain obligations we have regarding the use and disclosure of PHI.

Our Pledge Regarding Protected Health Information

We understand that health information about you and your health is personal. We are committed to protecting health information about you. We create a record of the products and services that we provide to you. We need this record to provide you with quality products and services used in your care and to comply with certain legal requirements. This notice applies to all of the PHI we use and disclose related to the products and services used in your care. Your personal doctor, health care provider, and other entities providing products or services to you may have different policies or notices regarding their use and disclosure of your PHI.

Our Legal Requirements

We are required by law to:

- Make sure that health information that identifies you is kept private;
- Give you this notice of our legal duties and privacy practices with respect to PHI about you;
- Notify you if we are unable to agree to a requested restriction on how your information is used and disclosed;
- Accommodate reasonable requests that you may make to communicate PHI by alternative means or at alternative locations;
- Obtain your written authorization for purposes other than those listed below and permitted under law; and
- Follow the terms of the notice that currently is in effect.

Who Will Follow Our Privacy Practices

This notice describes Novocure's practices and that of all Novocure employees, staff, and other company personnel for US operations only.

These entities, sites, and locations follow the terms of this notice. Additionally, these entities, sites, and locations may share PHI with each for treatment, payment, or health care operations purposes described in this notice.

Your Rights Regarding Protected Health Information About You

You have the following rights regarding PHI we maintain about you:

Right to Inspect and Copy

You have the right to inspect and copy PHI that may be used to make decisions about your care. Usually this includes medical and billing records. To inspect and copy PHI that may be used to make decisions about you, please contact 855-281-9301 or **support@novocure.com**. We may charge a fee for copying requested files. We may deny your request to inspect and copy in certain circumstances. If you are denied access to PHI, you may request that the denial be reviewed. Another person chosen by us will review your request and the denial. We will comply with the outcome of that review.

Right to Amend

If you feel that PHI we have about you is incorrect or incomplete, you may ask us to amend the information. You have the right to request an amendment for as long as the information is kept by us. To request an amendment, please contact 855-281-9301 or **support@novocure.com**. You must provide a reason that supports your request. We may deny your request for an amendment if it does not include a reason to support that request. Additionally, we may deny your request if you ask us to amend information that:

- Was not created by us, unless the person or entity that created the information is no longer available to make the amendment;
- Is not part of the PHI kept by or for us;
- Is not part of the information which you would be permitted to inspect and copy; or
- Is accurate and complete.

Right to Accounting of Disclosures

You have the right to request an "accounting of disclosures." This accounting is a list of the disclosures we made of PHI about you. Novocure™ will provide an accounting of all but the following types of disclosure:

- Those made for treatment, payment and health care operations;
- Those made to you about your own PHI;
- Those made to persons involved in your care or other notification purposes;
- Those made pursuant to an authorization signed by you disclosing specific uses and disclosures;
- Where the disclosures are part of a Limited Data Set (as defined in the Health Insurance Portability and Accountability Act);
- Where the disclosures are incidental to an otherwise permissible disclosure;
- For national security or intelligence purposes; and
- To correctional institutions or law enforcement custodial situations.

To request this list or accounting of disclosures, please contact 855-281-9301 or **support@novocure.com**. We may request that you submit the request in writing. Your request must state a time period that may not be longer than six years from the date of service. Your request should indicate in what form you want the list (i.e., paper or electronic). The first list you request within a 12-month period will be free. For additional lists, we will charge you for the costs of providing the lists. We will notify you of the costs involved and you may choose to withdraw or modify your request at the time before any costs are incurred.

Right to Request Restrictions

You have the right to request a restriction or limitation on the PHI we use or disclose about you for treatment, payment, or health care operations. You also have the right to request a limit on the PHI we disclose about you to someone who is involved in your care or the payment for your care, like a family member or friend. You may restrict disclosures of PHI to a health plan if you have paid out of pocket in full for the health care item or service. We are not required to agree to your request. If we do agree, we will comply with your request unless the information is needed to provide you emergency treatment. Please contact 855-281-9301 or **support@novocure.com** to request restrictions. We may request a written request. You must tell us i) what information you want to limit, ii) whether you want to limit our use, disclosure, or both, and iii) to whom you want the limits to apply, for example, disclosures to your spouse.

Right to Request Confidential Communications

You have the right to request that we communicate with you about medical matters in a certain way or at a certain location. For example, you can ask that we only contact you at work or by mail. Please contact 855-281-9301 or **support@novocure.com** to request confidential communications. We may request a written request. We will accommodate all reasonable requests. Your request must specify how or where you wish to be contacted.

Right to Revoke Authorization

You have the right, in those instances where written authorization is required, to revoke such authorization to use or disclose PHI except to the extent action has already been taken. Such revocation must be in writing.

Right to a Paper Copy of This Notice

You have the right to a paper copy of this notice. You may ask us to give you a copy of this notice at any time. Even if you have agreed to receive this notice electronically, you are still entitled to a paper copy of this notice. Please contact 855-281-9301 or **support@novocure.com** to request a paper copy.

How We May Use and Disclose Protected Health Information About You

The following categories describe different ways that we are permitted to use and disclose PHI as a health care provider. Certain of these categories may not apply to our business and we may not actually use or disclose your PHI for such purposes. Not every use or disclosure in a category will be listed. However, all of the ways we are permitted or required to use and disclose PHI, without your authorization, will fall within one of the categories.

For Treatment

We may use or disclose PHI about you to assist health care professionals and providers to provide you with medical treatment or services. For example, we may provide PHI related to your use of our products or services to your physician and the staff at your physician's practice to assist your physician in maintaining appropriate use of the device.

For Payment

We may use and disclose PHI about you so that the products and services we provide you may be billed to and payment may be collected from you, an insurance company, or a third party. For example, we may need to receive from or disclose to your health plan, Medicare, or the medical facility you resided in information about the products and services we provided to you so they or another responsible payor can pay us. This may specifically include information required for the

Prescription Order Form, Assignment of Benefits, MRIs, and medical record information. We may also tell your health care provider or plan about a product or service you are going to receive to obtain prior approval or to determine whether your provider or plan will cover that product or service.

For Marketing Purposes

At times, Novocure™, may, for the benefit of the clients, patients and market it serves, issue information, solicitations for fundraising or marketing materials on its products and services. Your rights under the Privacy rule include your ability to request restrictions or revoke the inclusion of your information at any time in all communications as well as opting into or opting out of any marketing or fundraising activities, uses and disclosures of PHI for marketing purposes, including subsidized treatment communications; disclosures that constitute a sale of PHI; and other uses and disclosures not described in this Privacy Notice or allowed by the Privacy rule.

For Health Care Operations

We may use and disclose PHI about you for our health care operations and we may use and disclose PHI about you to other health care providers involved in your care for certain health care operations they have to undertake. These uses and disclosures are necessary to run our company and make sure that users of our products receive the most cost-effective and therapeutic products possible. Examples of health care operations activities by Novocure include, but are not limited to: delivery, pick-up, and service functions; collection efforts; internal auditing; business planning (including analysis of product length of use, utility, or development/improvement of reimbursement methods or policy); assessing the quality of care and outcomes in your case and similar cases; and quality assurance/improvement activities. We may also combine PHI about many patients to decide what additional products and services we should offer, what products and services are not needed, and to justify how effective our products are in the care of individuals such as you. We may also disclose information to medical facilities and independent researchers for review and learning purposes. We may remove information that identifies you from this set of PHI so others may use it to study health care and health care delivery without learning who the specific patients are.

Notice/Reminders

We may use and disclose PHI to contact you or arrange for your health care provider to contact you regarding product delivery, maintenance, in-service, or pick-up.

Individuals Involved in Your Care or Payment for Your Care

We may disclose to a family member, other relative, close personal friend of yours, or any other person identified by you PHI directly relevant to such person's involvement with your care or payment for your health care when you are present for, or otherwise available prior to, a disclosure and you are able to make health care decisions, if: (i) we obtain your agreement; (ii) we provide you with the opportunity to object to the disclosure and you failed to do so; or (iii) we infer from the circumstances, based upon professional judgment, that you do not object to the disclosure. We may obtain your oral agreement or disagreement to a disclosure. However, if you are not present, or the opportunity to agree or object to the disclosure cannot practicably be provided because of your incapacity or an emergency circumstance, we may, in the exercise of professional judgment, determine whether the disclosure is in your best interests, and, if so, disclose only PHI that is directly relevant to the person's involvement with your health care.

Research

Under certain circumstances, we may use and disclose PHI about you for research purposes. For example, a research project may involve comparing the health and recovery of all patients who received a product or service for the same condition. We may also disclose PHI about you to people preparing to conduct a research project, for example to help them look for patients with specific medical circumstances. We will in most circumstances ask for your specific authorization if the researcher will have access to your name, address or other identifying information that reveals who you are.

As Required by Law

We will disclose PHI about you when required to do so by federal, state, or local law. For example, we may disclose information for judicial and administrative proceedings pursuant to legal authority; to report information related to victims of abuse, neglect or domestic violence; or to assist law enforcement officials in their law enforcement duties.

Government Functions

We may use and disclose PHI about you as required for specialized government functions such as protection of public officials, reporting to various branches of the armed services or national security activities authorized by law.

To Avert a Serious Threat to Health or Safety

We may use and disclose PHI about you when necessary to prevent a serious threat to your health and safety or the health and safety of the public or another person. Any disclosure, however, would only be to someone able to help prevent the threat.

Business Transfers

There may arise in the course of business the acquisition or sale of our business assets (Business Transfers). Such Business Transfers may involve the sale or purchase of PHI. Also, in the event that Novocure™ Inc. or its parent entity, Novocure Limited of Jersey (Channel Islands), or any subsidiary of Novocure Limited are acquired or substantially all of its assets are acquired, PHI likely will be one of the transferred assets.

Workers' Compensation

We may release PHI about you for workers' compensation or similar programs. These programs provide benefits for work-related injuries or illness.

Public Health Activities

We may use or disclose your PHI to a health oversight agency for activities authorized by law. These oversight activities include, for example, audits, investigations, inspections, and licensure. These activities are necessary for the government to monitor the health care system, government programs, and compliance with civil rights laws.

Lawsuits and Disputes

If you are involved in a lawsuit or a dispute, we may disclose PHI about you in response to a court or administrative order. We may also disclose PHI about you in response to a subpoena, discovery request, or other lawful process by someone else involved in the dispute, but only if efforts have been made to tell you about the request and obtain your written authorization or to obtain an order protecting the information requested.

Other Uses of Protected Health Information

Other uses and disclosures of PHI not covered by this notice or otherwise permitted by laws that apply to us will be made only with your written authorization. Your authorization will not be required if Novocure™ uses or discloses health information for purposes other than as covered by this notice or permitted by law if Novocure removes any information that individually identifies you before disclosing the remaining information. If you provide us authorization to use or disclose PHI about you, you may revoke that permission, in writing, at any time. If you revoke your permission, we will no longer use or disclose PHI about you for the reasons covered by your written authorization. You understand that we are unable to take back any disclosures we have already made with your permission, and that we are required to retain our records of the products and services that we provided to you.

Changes to This Notice

We reserve the right to change our information practices and to make the new provisions effective for all PHI we maintain. We also reserve the right to change this notice at any time. We reserve the right to make the revised or changed notice effective for PHI we already have about you as well as any information we receive in the future. You may request the current version of our privacy practices by contacting 855-281-9301 or **support@novocure.com**.

Complaints

If you believe your privacy rights have been violated, you may file a complaint with us or with the Secretary of the Department of Health and Human Services. To file a complaint with us, you must submit it in writing to Novocure. Please contact 855-281-9301 or **support@novocure.com** to request the current mailing instructions for Novocure.

Patient Bill of Rights

Your Rights

As a patient you have certain rights including, but not limited to, the following:

- **Information**. Patients have the right to receive accurate, easily understood information to assist them in making informed choices.
- **Choice**. Patients have the right to a choice of health care providers.
- **Access to Emergency Services**. Patients have the right to access emergency health services when and where the need arises.
- **Being a Full Partner in Health Care Decisions**. Patients have the right to participate fully in all decisions related to their health care.
- **Care Without Discrimination**. Patients have the right to considerate, respectful care from all members of the health care industry at all times and under all circumstances.
- **Privacy**. Patients have the right to communication with health care providers in confidence and to have the confidentiality of their individual identifiable health care information protected.
- **Speedy Complaint Resolution**. Patients have the right to a fair and efficient process for resolving differences.

Your Responsibilities

As a patient you have certain responsibilities including, but not limited to, the following:

- **Provide information.** You must give accurate and complete health information concerning your past illnesses, hospital stays, medications, allergies, and other pertinent items. You are also responsible for providing documentation required by your insurance company.
- **Ask questions.** You must ask questions when you do not understand medical conditions, equipment, instructions, and/or medical terminology.
- **Follow Instructions.** You must adhere to your developed and updated treatment plans.
- **Accept consequences.** You must accept consequences for not following the treatment plan instructions of your doctor and nurse.
- **Understand your benefits.** You must understand what your insurance company will or will not authorize for durable medical equipment (DME) benefits.
- **Product responsibilities.** Your doctor has prescribed this medical device for the treatment and care of your disease. This is a rental device and cannot be resold. Prompt return of this device is required once therapy is completed.
- **Show respect and consideration.** You must show respect and consideration to those who are assisting you in your treatment plan, including Novocure's staff providing technical support for your use of the device.
- **Meet financial commitments.** You are responsible for any applicable co-insurance, co-payments, or private pay amounts not covered by your insurance provider.

Contact Information for Questions or Complaints

Any questions, concerns or complaints may be addressed to: 855-281-9301 (toll-free) or **support@novocure.com.**

You may contact the Accreditation Commission for Health Care to report any concerns or register a complaint by calling ACHC toll-free at 855-937-2242 or 919-785-1214 and request the Complaints Department.

Authorization to Release Information; Assignment of Benefits; Acknowledgment of Education and Training; Acknowledgment of Receipt of Certain Forms; and Delivery Confirmation

Background

Optune® (the "System") is comprised of two main components: (1) an Electric Field Generator (the "Device"); and (2) INE Transducer Arrays (the "Arrays") that are disposable supplies to the Device. Novocure™ Inc. is referred to as "we" or "Novocure" in this service agreement ("Service Agreement"). The use of "you" in this Service Agreement refers to the patient named in this Service Agreement.

Authorization to Release Information

You authorize your physician and the practice, facility, and hospital of your physician, and any other holder of medical information about conditions for which you are being treated to release to Novocure any information necessary for treatment, payment, and health care operations related to your use of the System. You also authorize Novocure, your physician and the practice, facility, and hospital of your physician, and any other holder of medical information about conditions for which you are being treated to release such information to your insurance company and any other entity paying for your medical care ("your payor"). These authorizations apply to your current physician and previous physicians, their practices, facilities, and hospitals.

Authorization to Discuss Care

You authorize Novocure to discuss your care with the family members and/or caregivers listed below. You may revoke this authorization at any time by calling or emailing Novocure at 855-281-9301 or **support@novocure.com**.

List all authorized individuals: 920-203-5637
Barb Christenson

Assignment of Benefits

You give Novocure the right to bill for and receive payments for your medical care and you direct your payor to pay Novocure directly for the System. You agree to forward all payments to Novocure in the event that your payor pays you directly, and you acknowledge that Novocure may stop supplying the System to you if you fail to do so. You acknowledge receipt of the supply terms and information on financial responsibilities and warranties ("Supply Terms") from Novocure and agree to those terms.

Acknowledgment of Education and Training

You have received education on the use and maintenance of the System. You have been provided a technical support phone number for questions about use of the System. You have been provided with the User Manual for the System. You consent to accept phone calls from Novocure for technical support and health care operations matters, including billing matters.

Acknowledgment of Certain Forms

You acknowledge that you have received, read, and accepted all terms and conditions set forth in these documents:

1. **Patient Information Form**, which includes a Statement of Privacy Practices, Patient Bill of Rights, and Contact Information for Novocure for Questions and/or Complaints

   We are required by regulation to respond to your complaints within 5 calendar days and respond back to you with the results of our investigation within 14 calendar days.

2. **Supply Terms**, which includes Financial Responsibilities and Warranty information

3. **Advanced Beneficiary Notice** (for Medicare patients only)

The products and/or services provided to you by Novocure are subject to the supplier standards contained in the Federal regulations shown at 42 Code of Federal Regulations Section 424.57©. These standards concern business professional and operational matters (e.g., honoring warranties and hours of operation). The full text of these standards can be obtained at ***http://www.palmettogba.com/Palmetto/Providers.Nsf/files/supplierstandards30.pdf/$File/supplierstandards30.pdf****. Upon request we will furnish you a written copy of the standards.*

Please sign here:
David Christenson 10/3/2016
Signature Date

Printed on: 03 Oct 2016, 08:39:35 am; Printed by: NNEWBERG.

Delivery Confirmation

You acknowledge receipt of the equipment and supplies listed below

Part Description	Quantity	S/N or Lot Number
Optune® Device E0766	1	TFH 201213
Connection Cable	2	CAD 202632 CAD 202717
Portable Charger	1	1CH 200392
Power Supply	1	SPS 201481
Portable Battery	4	1BH 203709 1BH 203882 1BH 203716 1BH 205749
Black Transducer Array (Lot#) E0766	20	C1606403
White Transducer Array (Lot#) E0766	20	C1608902
Device Combo Bag	1	
Power Cord	2	
Manual – Instructions For Use	1	
Operation Manual	1	
Self-Exchange Kit	1	

You agree to the terms of this Service Agreement and of the related forms that you have received.
The authorizations granted in this Service Agreement will expire two (2) years from the date signed below.

Signatures

Patient Name (please print): David Christenson

Patient or Authorized Signature: David Christenson Date: 10/3/2016

If anyone other than patient completes or signs this form, please enter the following information:

Name: Telephone Number:

Address:

City, State, ZIP:

Relationship to Patient:

Reason for Signing:

For Novocure™ Use Only

Delivery Person/Service Print: Nancy Newberg

Signature/Tracking#: Nancy Newberg

Delivery Date: 10/3/16

Novocure Patient ID#: 1013346

Novocure Order #: 26585

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OPTUNE™ | PATIENT INFORMATION AND CONSENT

Optune™ Treatment Education Visit

IMPORTANT: Please do not sign this consent until you read and understand the consent. Please discuss any questions you may have with the Novocure™ personnel that will conduct your treatment education. You should feel that signing this form is something you are doing voluntarily. If you feel that you are under pressure, please do not sign this form. Please read this consent to understand the purpose and nature of this treatment education visit. If you sign this consent, you confirm that you understand the purpose and nature of this visit and that you give your consent to participate in the treatment education.

You or your physician has requested that Novocure personnel conduct a treatment education visit for Optune. ***If you want to hold this session at your physician's office, please tell Novocure personnel prior to the start of the session and do not sign this consent.***

You (and your caregiver(s)) are being trained regarding the use of Optune. As part of this session, you will be taught about the following:

- Use of Optune, including how to change the battery, how to recharge the battery and connect to an external power supply, how to connect the transducer arrays connectors to the connector box, and what to do when an alarm occurs;
- How to shave your head to maintain appropriate transducer array contact with your scalp;
- How to apply the transducer arrays to your scalp; and
- How to turn Optune "on" and "off"

By signing this consent, you confirm your understanding that:

- Novocure personnel conducting your treatment education session are not physicians or healthcare providers. Please talk to your physician regarding your medical care and any questions you may have regarding your medical condition and your treatment options
- Novocure personnel are providing education regarding the use of Optune. You will also receive the Patient Instruction and Operation Manual (PIOM) for Optune, which will be a resource for any questions you may have after this session
- Novocure personnel will teach you and/or your caregiver(s) how to shave your head and apply the transducer arrays. You and/or your caregiver(s) will shave your head and apply the transducer arrays, with assistance from Novocure personnel. Novocure personnel may touch you during the session while teaching you and/or your caregiver(s) to perform these activities
  - *You may suffer cuts and possible skin irritation associated with shaving your head*
  - *You may suffer mild to moderate skin irritation associated with application of the transducer arrays*
  - *You should contact your physician regarding care for any injury you suffer during this treatment education session*

- Novocure personnel will show you and/or your caregiver(s) how to begin therapy by turning Optune "on." It is your decision when to begin Optune therapy. If you initiate therapy today, please initiate therapy in the presence of Novocure personnel, who will confirm Optune is working appropriately.
- If you have a medical issue during the session, you consent to Novocure personnel calling 911 and/or emergency medical services.
- Your physician will confirm that you understand how to use Optune and its use at your next physician visit.

I agree to participate in the treatment education session described and to allow Novocure personnel to conduct the session.

By signing this form, I have not given up any of my legal rights.

Please print your name: David Christenson

10/3/2016 David Christenson

(Date) (Signature of Participant)

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Patient Document Acknowledgement

Document	*Initials*
1. Service Agreement	DC
2. Patient Rights and Responsibilities (From service agreement)	DC
3. Supplier Standards (Medicare only)	
4. Financial review/Assessment (Patient was contacted and these items discussed)	DC
5. How to file a complaint	DC

This form is to be returned to the Commercial Operations Center along with the signed Service Agreement.

Technical Review of Optune®

Patient Name: David Christenson	Patient #: 1013346
Patient Signature: David Christenson	Date: 10/3/2016

Optune® ☑
- Overview and Description
- Powering On/Off

Powering the Device ☑
- Portable Batteries
- Connecting Power Sources
- Charging Portable Batteries
- Battery Charger
- Plug-In Power Supply

Transducer Arrays ☑
- Overview and Description
- Transducer Array Components
- Placement Recommendations
- How to Shift Paired Arrays at Each Array Change
- Skin Observation and Care
- Showering
- Disposal and Reorder

Connection Cable ☑
- Overview and Description
- Connecting to Device

Carrier Bag ☑
- Placement and Carry Options

Troubleshooting ☑
- Errors
- Common Causes
- Correcting Errors
- nCompass™ Support Information
- Equipment Exchange Process

Placing the Arrays ☑
- Preparing the Head
- Review NovoTAL Map
- Applying the Transducer Arrays

Patient Literature ☑
- Patient Information and Operation Manual
- Patient Quick Start Guide

Novocure Employee Name: Nancy Newberg	
Novocure Employee Signature: Nancy Newberg	Date: 10/3/16

novocure

TM-MA-002 Rev 07 PAGE 1 of 1

ASCENSION NE WI ST. ELIZABETH HOSPITAL, APPLETON, WI
RADIATION ONCOLOGY

PATIENT NAME:	CHRISTENSON, DAVID P	ADMIT DATE:	09/19/18
PROVIDER:	DAVIS MD, RICK D	REPORT NO:	0922-0008

DATE OF SERVICE: 09/19/2018

FOLLOWUP NOTE FROM RADIATION ONCOLOGY CLINIC

REFERRING PHYSICIAN: Karen Gremminger, M.D.

DIAGNOSIS: Glioblastoma of the right occipital lobe. Grade is IV. Stage is not applicable. The patient's radiation therapy delivered included VMAT and IMRT to the brain on 08/17/2015, received 6000 cGy in 30 fractions, 200 cGy each, completed that on 09/28/2015. He later received a single fraction SRS within the right occipital tumor bed receiving 24 Gy in a single fraction on 01/13/2016. Currently, he is on optimum therapy. Previous visit was 06/27/2018.

INTERVAL HISTORY: The patient has had no change in his clinical status. He has no new neurologic status, no side effects. He continues to wear his Optune roughly 18 hours a day or more. They do receive updates on compliance from the Optune therapy company. An MRI of the brain done on 09/18/2018, showed stable postoperative findings. No evidence of tumor recurrence or progression. No change in T2-FLAIR signal.

REVIEWED MEDICATIONS: He is on Decadron 1 mg a day, aspirin, docusate sodium, Coumadin and acetaminophen as needed.

ALLERGIES: NO KNOWN ALLERGIES.

REVIEW OF SYSTEMS: Complete 12 system review done and intake reviewed with the patient and updated the record as needed. Pain is 0/10. Remainder of his review of systems is within normal limits. ECOG status is 0. Advanced directives completed and in place.

PHYSICAL EXAMINATION: Age appropriate male. He is wearing his Optune device on his head with associated wires and pads. Otherwise, no significant irregularities in the patient. His height is 76 inches, weight is 228 pounds. BMI is 27.8. He is appropriately counseled about this. Temperature 98.1, heart rate 56, respiratory rate is 16, blood pressure 130/60, O2 sat 97%. Brief survey of neurologic function and cranial nerves are normal. He has no abnormalities in his balance or ambulation. No further exam was performed other than noting. His mentation is excellent.

IMPRESSION: Glioblastoma in the right occipital area. The patient is post primary therapy with temozolomide and external beam radiation therapy. He had recurrence in the surgical bed roughly four months later that was treated with radiosurgery. He was then started on Optune therapy and has been stable, if not improved in his imaging since that time. He has no current concerns or problems.

CHRISTENSON, DAVID P
MRN: E000369357
ACCT: E34723117 REG CLI
DOB: 11/14/53
DEPT: E.DICT

ASCENSION NE WI ST. ELIZABETH HOSPITAL, APPLETON, WI
RADIATION ONCOLOGY

PATIENT NAME: CHRISTENSON, DAVID P REPORT NO: 0922-0008

PLAN: He will continue on Optune therapy indefinitely. There is no data on circumstance in which this can be discontinued. He will be doing some traveling to Europe in the near future and we will have a one week break from his Optune therapy. During that period, he will reinstitute upon return. I will plan on seeing him back in 3 months with an MRI of the brain plus contrast prior to that visit. All questions were answered today.

Greater than 15 minutes, greater than 50% being counseling and coordination of care.

JOB ID: 176857
cc:
Trans: R1

Rick D. Davis, MD
Radiation Oncology
St. Elizabeth Hospital Cancer Center

Electronically Signed: RICK D DAVIS MD 10/11/18 0839

FINAL ORIGINAL IN COMPUTER PATIENT RECORD

CHRISTENSON, DAVID P
MRN: E000369357
ACCT: E34723117 REG CLI
DOB: 11/14/53
DEPT: E.DICT

DEPARTMENT OF RADIOLOGY

	D.O.B	AGE	SEX	EXAM DATE
CHRISTENSON,DAVID P	11/14/1953	64	M	09/18/18

LOC: M.RAD
Pt Ph#: 920-203-5636
MR#: 0000343818
Ordered By: DAVIS MD,RICK D
ACCT# 003754608
Status: REG CLI

EXAM#	TYPE/EXAM	RESULT
002857789	MRI/HEAD W/WO CONTRAST	

RICK D DAVIS, MD

HEAD W/WO CONTRAST

COMPARISON: MRI brain study with and without contrast dated 6/18/2018

HISTORY: Three-month follow-up.

TECHNIQUE: MRI of the brain was performed before and after intravenous administration of 10 mL of MultiHance gadolinium contrast.

FINDINGS:
BRAIN AND CSF SPACES: Postoperative findings of right craniotomy for tumor resection. Unchanged heterogeneous enhancement involving the right parietal occipital resection cavity extending to the right occipital and peritrigonal white matter. Unchanged FLAIR hyperintense signal surrounding the resection cavity and extending throughout the posterior right frontal, parietal, occipital and temporal lobes extension as well as extension into the external and internal capsules. FLAIR hyperintense signal extends across the right splenium of the corpus callosum. Unchanged FLAIR hyperintense signal in the left periventricular white matter scattered small foci of FLAIR hyperintense signal scattered throughout the white matter both cerebral hemispheres. Unchanged effacement of the right lateral ventricle. Slightly decreased effacement of the third ventricle with midline shift to the left of 4 mm. Susceptibility weighted images demonstrate hemosiderin staining associated with the resection cavity with scattered small foci in the right parietal lobe. Unchanged diffusion abnormality associated with the FLAIR hyperintense signal in the right splenium.
PITUITARY: Normal.
PINEAL: Normal.
VASCULATURE: Normal.
ORBITS: Normal.
NASAL CAVITY AND NASOPHARYNX: Normal.
PARANASAL SINUSES: There is patchy mucosal thickening of the ethmoid sinuses.
OTOMASTOID FINDINGS: Mastoid air cells are clear.
SKULL AND C-SPINE: Normal.

IMPRESSION:

DEPARTMENT OF RADIOLOGY

CHRISTENSON, DAVID P

D.O.B	AGE	SEX	EXAM DATE
11/14/1953	64	M	09/18/18

LOC: M.RAD
Pt Ph#: 920-203-5636
MR#: 0000343818
ACCT# 003754608
Status: REG CLI

Ordered By: DAVIS MD, RICK D

EXAM#	TYPE/EXAM	RESULT
002857789	MRI/HEAD W/WO CONTRAST	

1. Stable postoperative findings of right craniotomy for right occipital tumor resection with unchanged appearance of the heterogeneously enhancing resection cavity. No evidence of tumor progression.

2. FLAIR hyperintense signal surrounding the resection cavity and extending throughout the right cerebral hemisphere as detailed above. Unchanged mass effect with 4 mm midline shift to the left.

Lisa D. Roller, MD
Division of Neuroradiology
Radiology Associates of the Fox Valley, S.C.

RAFVCC
I.2

Electronically Signed By: Lisa Roller, MD
Signed Date/Time: 9/19/2018 8:11 AM

** REPORT SIGNED IN OTHER VENDOR SYSTEM 09/19/2018 **
Reported By: ROLLER, LISA MD

CC: DAVIS MD, RICK D

Edited Date: 09/19/18 by PROVIDER
Printed Date/Time: 10/29/2018 (1241)

Version 1.2018
March 20, 2018

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Central Nervous System Cancers

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Anaplastic Gliomas[a]/Glioblastoma

GLIOBLASTOMA PATHOLOGY[d] → **MGMT[q] PROMOTER STATUS** → **ADJUVANT TREATMENT** → **FOLLOW-UP[b]**

- Glioblastoma[f]
  - Age ≤70 y
    - Good performance status (KPS ≥60)
      - Methylated →
        - Consider clinical trial (preferred for eligible patients)
        - or
        - Standard brain RT[l] + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy (category 1)[n,r,s,t]
        - or
        - Standard brain RT[l] + concurrent temozolomide and adjuvant temozolomide (category 1)[n,r,s]
      - Unmethylated or indeterminate →
        - Consider clinical trial (preferred for eligible patients)
        - or
        - Standard brain RT[l] + concurrent temozolomide[u] and adjuvant temozolomide[u] + alternating electric field therapy (category 1)[n,r,s,t]
        - or
        - Standard brain RT[l] + concurrent temozolomide[u] and adjuvant temozolomide (category 1)[n,r,s,u]
        - or
        - Standard brain RT alone[l]
    - Poor performance status (KPS <60) →
      - Hypofractionated brain RT[l] (preferred) ± concurrent or adjuvant TMZ
      - or
      - Temozolomide[o]
      - or
      - Palliative/Best supportive care
  - Age >70 y → See GLIO-4

Adjuvant treatment → Brain MRI 2–6 wk after RT,[p] then every 2–4 mo for 3 y, then every 6 mo indefinitely → See Recurrence (GLIO-5)

[a]This pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[d]See Principles of Brain Tumor Pathology (BRAIN-F).
[f]This pathway also includes gliosarcoma.
[l]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[o]Consider temozolomide if tumor is MGMT promoter methylated
[p]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.
[q]MGMT= O^6-methylguanine-DNA methyltransferase.
[r]Combination of agents may lead to increased toxicity or radiographic changes
[s]Benefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown
[t]Alternating electric field therapy is only an option for patients with supratentorial disease.
[u]Clinical benefit from temozolomide is likely to be lower in patients whose tumors lack MGMT promoter methylation.

All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Anaplastic Gliomas[a]/Glioblastoma

GLIOBLASTOMA PATHOLOGY[d] → **MGMT PROMOTER STATUS[q]** → **ADJUVANT TREATMENT** → **FOLLOW-UP[b]**

- Age >70 y Glioblastoma[j]
  - Good performance status (KPS ≥60)
    - Methylated →
      - Consider clinical trial (preferred for eligible patients)
      - or Hypofractionated brain RT[l] + concurrent and adjuvant temozolomide (category 1)[n,r,s]
      - or Standard RT[l] + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy (category 1)[n,r,s,t]
      - or Standard RT[l] + concurrent temozolomide and adjuvant temozolomide[n,r,s]
      - or Temozolomide
      - or Hypofractionated brain RT alone[l]
    - Unmethylated or indeterminate →
      - Consider clinical trial (preferred for eligible patients)
      - or Hypofractionated brain RT[l] + concurrent and adjuvant temozolomide[n,r,s]
      - or Standard RT[l] + concurrent temozolomide[u] and adjuvant temozolomide[u] + alternating electric field therapy (category 1)[n,r,s,t]
      - or Standard RT[l] + concurrent temozolomide[u] and adjuvant temozolomide[n,r,s,u]
      - or Hypofractionated brain RT alone[l]
  - Poor performance status (KPS <60) →
    - Hypofractionated brain RT alone[l]
    - or Temozolomide[o]
    - or Palliative/Best supportive care

→ Brain MRI 2–6 wk after RT,[p] then every 2–4 mo for 3 y, then every 6 mo indefinitely → See Recurrence (GLIO-5)

See footnotes on GLIO-4A

All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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RECURRENCE				TREATMENT[w]	
Recurrent disease[x,p] for: • Anaplastic oligodendroglioma • Anaplastic oligoastrocytoma, NOS[k] • Anaplastic astrocytoma • Anaplastic gliomas • Glioblastoma	Diffuse or multiple		→	Consider clinical trials (preferred for eligible patients) or Palliative/Best supportive care if poor performance status or Systemic chemotherapy[n,y] or Surgery for symptomatic, large lesion or Consider alternating electric field therapy for glioblastoma (category 2B)	→ Palliative/Best supportive care See NCCN Guidelines For Palliative Care
	Local	Resectable → Consider clinical trial or Resection[v]	→ Brain MRI[b,j] →	Consider clinical trials (preferred for eligible patients) or Palliative/Best supportive care if poor performance status or Systemic chemotherapy[n,y] or Consider reirradiation (category 2B)[l,z] or Consider alternating electric field therapy for glioblastoma (category 2B)	→ Palliative/Best supportive care See NCCN Guidelines For Palliative Care
	Local	Unresectable or resection not recommended/ elected	→	(same as above)	

[a]This pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[j]Postoperative brain MRI within 24–72 hours after surgery.
[k]The 2016 WHO Classification of Tumors of the CNS has deleted oligoastrocytoma as a category, although "anaplastic oligoastrocytoma, NOS" may continue to be used for 1) patients with mixed histology and no available molecular data (ie, no tissue available for analysis) for determining whether to classify as oligodendroglioma versus astrocytoma; or 2) rare instances in which the tumor has regions with histologic features of oligoastrocytoma with 1p19q-codeletion, and distinct regions with histologic features of astrocytoma without 1p19q-codeletion.
[l]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[p]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.
[v]Consider carmustine (BCNU) wafer implant during resection. Treatment with carmustine wafer may impact enrollment in clinical trials.
[w]The efficacy of standard-of-care treatment for recurrent glioblastoma is suboptimal, so for eligible patients consideration of clinical trials is highly encouraged. Prior treatment may impact enrollment in clinical trials.
[x]Consider biopsy, MR spectroscopy, MR perfusion, brain PET/CT, or brain PET/MRI, or re-image to follow changes that may be due to progression versus radionecrosis.
[y]Anaplastic oligodendrogliomas have been reported to be especially sensitive to chemotherapy. Chemotherapy using temozolomide or nitrosourea-based regimens may be appropriate.
[z]Especially if long interval since prior RT and/or if there was a good response to prior RT.

Note: All recommendations are category 2A unless indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

[redacted]

JAMA Oncology | Original Investigation

Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma
A Secondary Analysis of a Randomized Clinical Trial

Martin J. B. Taphoorn, MD; Linda Dirven, PhD; Andrew A. Kanner, MD; Gitit Lavy-Shahaf, PhD; Uri Weinberg, MD, PhD; Sophie Taillibert, MD; Steven A. Toms, MD; Jerome Honnorat, MD, PhD; Thomas C. Chen, MD, PhD; Jan Sroubek, MD; Carlos David, MD; Ahmed Idbaih, MD, PhD; Jacob C. Easaw, MD, PhD; Chae-Yong Kim, MD, PhD; Jordi Bruna, MD, PhD; Andreas F. Hottinger, MD, PhD; Yvonne Kew, MD, PhD; Patrick Roth, MD; Rajiv Desai, MD; John L. Villano, MD, PhD; Eilon D. Kirson, MD, PhD; Zvi Ram, MD; Roger Stupp, MD

Invited Commentary

Supplemental content

IMPORTANCE Tumor-treating fields (TTFields) therapy improves both progression-free and overall survival in patients with glioblastoma. There is a need to assess the influence of TTFields on patients' health-related quality of life (HRQoL).

OBJECTIVE To examine the association of TTFields therapy with progression-free survival and HRQoL among patients with glioblastoma.

DESIGN, SETTING, AND PARTICIPANTS This secondary analysis of EF-14, a phase 3 randomized clinical trial, compares TTFields and temozolomide or temozolomide alone in 695 patients with glioblastoma after completion of radiochemotherapy. Patients with glioblastoma were randomized 2:1 to combined treatment with TTFields and temozolomide or temozolomide alone. The study was conducted from July 2009 until November 2014, and patients were followed up through December 2016.

INTERVENTIONS Temozolomide, 150 to 200 mg/m^2/d, was given for 5 days during each 28-day cycle. TTFields were delivered continuously via 4 transducer arrays placed on the shaved scalp of patients and were connected to a portable medical device.

MAIN OUTCOMES AND MEASURES Primary study end point was progression-free survival; HRQoL was a predefined secondary end point, measured with questionnaires at baseline and every 3 months thereafter. Mean changes from baseline scores were evaluated, as well as scores over time. Deterioration-free survival and time to deterioration were assessed for each of 9 preselected scales and items.

RESULTS Of the 695 patients in the study, 639 (91.9%) completed the baseline HRQoL questionnaire. Of these patients, 437 (68.4%) were men; mean (SD) age, 54.8 (11.5) years. Health-related quality of life did not differ significantly between treatment arms except for itchy skin. Deterioration-free survival was significantly longer with TTFields for global health (4.8 vs 3.3 months; $P < .01$); physical (5.1 vs 3.7 months; $P < .01$) and emotional functioning (5.3 vs 3.9 months; $P < .01$); pain (5.6 vs 3.6 months; $P < .01$); and leg weakness (5.6 vs 3.9 months; $P < .01$), likely related to improved progression-free survival. Time to deterioration, reflecting the influence of treatment, did not differ significantly except for itchy skin (TTFields worse; 8.2 vs 14.4 months; $P < .001$) and pain (TTFields improved; 13.4 vs 12.1 months; $P < .01$). Role, social, and physical functioning were not affected by TTFields.

CONCLUSIONS AND RELEVANCE The addition of TTFields to standard treatment with temozolomide for patients with glioblastoma results in improved survival without a negative influence on HRQoL except for more itchy skin, an expected consequence from the transducer arrays.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00916409

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Martin J. B. Taphoorn, MD, PhD, Department of Neurology, Haaglanden Medical Center, PO BOX 2191, 2501 VC, The Hague, The Netherlands (m.taphoorn@haaglandenmc.nl).

Glioblastoma has a poor prognosis,[1,2] and, as tumors grow, patients often experience a progressive decline in neurologic function and health-related quality of life (HRQoL).[3-7] The current standard of care is not curative but results in prolongation of life. However, extension of survival is meaningful only if patients' functioning and well-being can be retained or improved.[8-11] Therefore, it is important to determine the net clinical benefit of each new treatment or treatment modality introduced; possible benefits of a new treatment, in terms of prolonged survival, have to be carefully weighed against potential negative effects of the treatment on the patients' quality of life.

The current standard of care for patients with newly diagnosed glioblastoma comprises surgical resection to the extent safely feasible followed by radiotherapy with concomitant and maintenance chemotherapy with temozolomide.[12] Tumor-treating fields (TTFields) (Optune; Novocure Ltd) is an antimitotic physical treatment modality[13,14] delivered by a home use medical device with wired transducer arrays placed on the patients' scalp. When added to standard maintenance temozolomide chemotherapy, TTFields has been demonstrated to improve both progression-free survival and overall survival in a randomized clinical trial (NCT00916409).[15]

Treatment with TTFields involves the patient carrying a mobile electrical device for more than 18 hours per day and having 4 arrays of transducers continuously fixed to the shaved scalp. Concerns regarding the influence of wearing the device on patients' HRQoL have therefore been raised.[16,17] The incidence of adverse events was not increased by the addition of TTFields to temozolomide therapy except for an expected mild to moderate skin irritation beneath the electrodes in 52% of pateints (severe in 2%). Herein, we report on the influence of treatment with TTFields on the patients' HRQoL, which was a predefined secondary objective of the randomized clinical trial. The present study was conducted from July 2009 until November 2014, and patients were followed up through December 2016.

Key Points

Question What is the influence of adding tumor-treating fields to the standard treatment on health-related quality of life in patients with glioblastoma?

Findings In this secondary analysis of the EF-14 randomized clinical trial, the addition of tumor-treating fields did not negatively influence health-related quality of life except for itchy skin, an expected consequence from the transducer arrays.

Meaning Tumor-treating field therapy has previously been shown to prolong both progression-free and overall survival. When considering the net clinical benefit, improved survival without a negative influence on health-related quality of life supports the addition of tumor-treating fields to standard treatment in patients with glioblastoma.

Methods

Study Population

Patients eligible for this study were aged 18 years or older, had newly diagnosed and histologically confirmed supratentorial glioblastoma (World Health Organization grade IV astrocytoma), were progression free after undergoing maximal safe debulking surgery or biopsy, and had completed standard radiotherapy with concomitant temozolomide. Patients were required to have a Karnofsky Performance Status score of at least 70 at the time of enrollment, corresponding to at least being able to perform self-care. Further details on the study population are available elsewhere.[15] All patients provided written informed consent, and the study was approved by the institutional review boards or ethics committees of all participating centers and the relevant competent authorities (eAppendix 1 in Supplement 1); the participants did not receive financial compensation.

Study Design and Treatment

This prospective, multicenter, open-label, randomized clinical phase 3 trial recruited 695 patients at 90 medical centers in North America, Europe, the Republic of Korea, and Israel. The trial protocol is available in Supplement 2. The trial was designed to test the efficacy of TTFields in combination with the best standard of care in the treatment of newly diagnosed glioblastoma (ie, radiotherapy with concomitant and adjuvant temozolomide). The primary end point was progression-free survival, with overall survival as a powered secondary end point. Health-related quality of life was a secondary end point. Patients who were progression free after completion of radiochemotherapy were randomized within 4 to 7 weeks at a ratio of 2:1 to receive standard maintenance temozolomide chemotherapy (150-200 mg/m^2 for 5 days every 28 days for 6 cycles) with or without the addition of TTFields. If tolerated well, TTField therapy was to be continued until the second progression or up to 2 years.

Patients in the TTFields plus temozolomide group received continuous TTFields combined with maintenance temozolomide. TTFields were delivered through a portable device in an outpatient setting. Patients receiving TTFields had 4 transducer arrays with 9 insulated electrodes each placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain. Although uninterrupted treatment was recommended, the patient could take short breaks if needed; patients were advised to continue treatment for at least 18 hours a day. More details on the study design and treatment are published elsewhere.[15]

HRQoL Assessment

The evaluation of HRQoL was performed using the validated European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30) and brain module (QLQ-BN20).[18-20] Questionnaires were completed on paper at baseline (prior to randomization) and subsequently every 3 months for up to 12 months. Nine scales and items were preselected as important based on relevance for patients with glioblastoma and hypothesized effects of the TTFields delivery device on patients' HRQoL: global health status; physical, cognitive, role, social, and emotional functioning; itchy skin;

pain; and weakness of legs. We hypothesized that any burden of carrying the device (on physical functioning and itchy skin) or detriment to social and role functioning due to the visibility of the therapy may be balanced by patients' feeling of well-being (global health status and emotional functioning) related to active participation of both the patient and the caregiver in the fight against cancer and increasing patient empowerment. Moreover, we hypothesized that treatment with TTFields would not have an influence on cognitive functioning, pain, and weakness of legs.

Statistical Analysis

Calculation of HRQoL Scores

The items on both questionnaires were scaled and scored using the recommended EORTC procedures.[21] Raw scores were transformed to a linear scale ranging from 0 to 100, with a higher score representing a higher level of functioning or higher level of symptoms. The results of this study are presented in accordance with guidelines for reporting HRQoL in cancer clinical trials and methods.[22-24] Differences of at least 10 points (on a 0-100 scale) were classified as the minimum clinically meaningful change in any HRQoL scale/item.[24]

Descriptive Statistics

Descriptive statistics were used to report HRQoL scores as well as the sociodemographic and clinical variables for the population of patients who completed at least 1 HRQoL scale at baseline separately for both treatment groups. Means and SDs or medians and ranges were calculated for continuous variables depending on the distribution of the variable. Frequencies and percentages were calculated for nominal variables. Differences between arms were tested using a 2-sided χ^2 test or an independent 2-tailed, unpaired t test or Mann-Whitney test at an α value of .05 for each variable.

Adherence to HRQoL assessments was calculated as the number of forms received divided by the number of forms expected at every assessment. Patients who completed the assessments at the time of progression were included in this analysis.

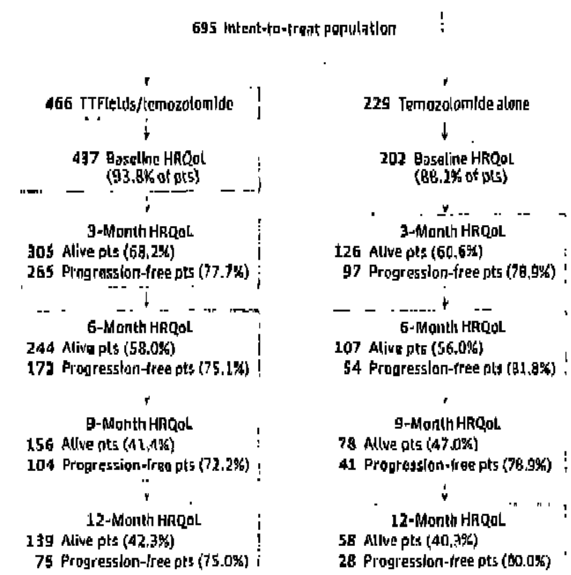
HRQoL Scores Over Time

Mean HRQoL scores over time were calculated as well as the mean changes from baseline. A stable HRQoL score was defined as a change of less than 10 points, and a change of 10 or more points indicated a deterioration or improvement depending on the scale or item. Mean change from baseline was plotted to evaluate the longitudinal course of patients' experience of disease and treatment, and a linear mixed-model repeated-measures analysis was used to estimate the treatment effect over time. A sensitivity analysis of complete cases using multiple imputations with a predictive mean matching regression model was used to check the robustness of the treatment effect over time. An additional sensitivity analysis used a repeated-measures model that assumes there is random variation among participants that is related to the time of dropout.

Stable or Improved HRQoL During the Progression-Free Period

The percentage of patients with stable (<10-point change) or improved (≥10-point change) HRQoL during the progression-free period, thus excluding the HRQoL assessment at progression, was determined separately for both treatment arms. This calculation was based on the total number of patients with a valid baseline HRQoL assessment and at least 1 additional follow-up assessment. Moreover, the area under the curve of stable or improved HRQoL for the entire duration of stability or improvement was determined, and differences between arms were assessed with the trapezoidal method (eAppendix 2 in Supplement 1).

Figure 1. Consort Diagram



Data are the number and percentage of patients in the categories (baseline, alive, and progression-free) who completed the health-related quality-of-life (HRQoL) questionnaire at the indicated times. pts indicates patients; TTFields, tumor-treating fields.

Deterioration-Free Survival and Time to Deterioration

Deterioration-free survival was defined as the time to a greater than 10-point deterioration in scores from baseline without a subsequent 10-point or more improvement in scores compared with baseline, progressive disease, or death in the absence of a previous definitive deterioration before the next assessment. Disease progression was included as a surrogate measure. Data were censored at the last HRQoL assessment date for patients with a change of less than 10 points, patients who did not progress, or patients who died after 9 weeks since the last assessment. Data for patients with missing baseline scores were not included, and patients missing all postbaseline HRQoL assessments were censored at randomization. Time to deterioration (TTD) was defined similarly to deterioration-free survival, with the exception that progressive disease was excluded as an event (ie, nonmissing HRQoL data beyond progression were included). Kaplan-Meier methodology was used to estimate deterioration-free survival and TTD distributions and median times, and 95% CIs were computed using the Greenwood formula. The difference between treatment arms

Table 1. Baseline Demographic and Disease Characteristics

Characteristic	TTFields Plus Temozolomide (n = 437)	Temozolomide (n = 202)	All Patients (N = 639)	P Value
Age, y				
Mean (SD)	54.6 (11.4)	55.2 (11.6)	54.8 (11.5)	.50
Median (range)	56.0 (19-83)	57.0 (19-80)	56.0 (19-83)	
Sex, No. (%)				
Male	297 (68.0)	140 (69.3)	437 (68.4)	.73
Female	140 (32.0)	62 (30.7)	202 (31.6)	
Antiepileptic medication at baseline, No. (%)	174 (39.8)	79 (39.1)	253 (39.6)	.87
Corticosteroid therapy at baseline, No. (%)	129 (29.5)	60 (29.7)	189 (29.6)	.96
Region, No. (%)				
United States	203 (46.5)	97 (48.0)	300 (46.9)	.71
Canada, Europe, Israel, and Korea	234 (53.5)	105 (52.0)	339 (53.1)	
Extent of resection, No. (%)				
Biopsy	55 (12.6)	24 (11.9)	79 (12.4)	
Partial resection	149 (34.1)	70 (34.7)	219 (34.3)	.97
Gross total resection	233 (53.3)	108 (53.5)	341 (53.4)	
Tumor position, No. (%)[a]				
Corpus callosum	23 (5.3)	12 (5.9)	35 (5.5)	
Frontal lobe	177 (40.5)	74 (36.6)	251 (39.3)	
Occipital lobe	55 (12.6)	24 (11.9)	79 (12.4)	.66
Parietal lobe	138 (31.6)	78 (38.6)	216 (33.8)	
Temporal lobe	179 (41.0)	81 (40.1)	260 (40.7)	
Missing	2 (<1)	2 (1.0)	4 (0.6)	
Tumor location, No. (%)[a]				
Left	202 (46.2)	84 (41.6)	286 (44.8)	
Right	234 (53.5)	116 (57.4)	350 (54.8)	.65
Both	4 (0.9)	2 (1.0)	6 (0.9)	
Corpus callosum	14 (3.2)	9 (4.5)	23 (3.6)	
Completed radiotherapy, No. (%)				
<57 Gy	20 (4.6)	10 (5.0)	30 (4.7)	
60 Gy (standard; ±5%)	399 (91.3)	188 (93.1)	587 (91.9)	.38
>63 Gy	15 (3.4)	3 (1.5)	18 (2.8)	
Missing	3 (0.7)	1 (0.5)	4 (0.6)	
Karnofsky performance score				
Median (range)	90 (60-100)	90 (70-100)	90 (60-100)	.26
Baseline Mini-Mental State Examination score available, No. (%)	429 (98.2)	194 (96.0)	623 (97.5)	
≤26	81 (18.9)	43 (22.2)	124 (19.9)	.34
27-30	348 (81.1)	151 (77.8)	499 (80.1)	
Cycles (months) of treatment with TTFields		NA	NA	NA
No.	425			
Mean (SD)	12.5 (11.8)			
Median (range)	8.3 (0-82)			
Cycles of treatment with temozolomide				
No.	430	192	622	
Mean (SD)	8.9 (8.3)	7.5 (6.2)	8.5 (7.8)	.02
Median (range)	6.2 (0-51)	5.5 (0-33)	5.9 (0-51)	
Adherence to TTFields therapy[b]	327 (74.8)	NA	NA	NA

Abbreviations: Gy, gray; NA, not applicable; TTFields, tumor-treating fields.

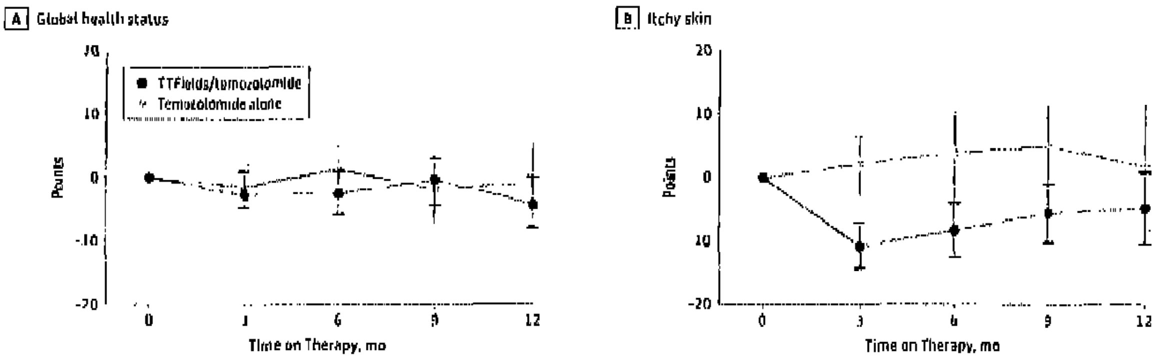
[a] Multiple locations possible.

[b] Defined as use of the device 75% or more of the time during the first 3 months of treatment.

was compared using a 2-sided stratified log-rank test. Hazard ratios were estimated using a stratified (for extent of resection and *MGMT* status) Cox proportional hazards regression model.

SAS, version 9.4 (SAS Institute) was used for all statistical analyses, and comparisons between groups were based on the intent-to-treat principle. *P* values <.05 were considered to be

Figure 2. Changes in Global Health Status and Itchy Skin



No. of patients	0	3	6	9	12
A: TTFields	435	295	237	151	133
A: Temozolomide	199	119	98	75	57
B: TTFields	427	284	230	145	131
B: Temozolomide	196	116	96	71	54

Mean changes in points on health-related quality of life scales from baseline in global health status (A) and itchy skin with (B) with tumor-treating fields (TTFields) plus temozolomide compared with temozolomide alone. No change, between 0 and 10 points; improvement and deterioration, changes of 10 points or more. Error bars indicate SD.

statistically significant. The Hochberg procedure was used to adjust for the multiplicity of treatment comparisons in the preselected HRQoL scales analyses.

Results

Patients

A total of 695 patients were randomly assigned in a 2:1 ratio to TTFields plus temozolomide (n = 466) or temozolomide alone (n = 229). A total of 639 (91.9%) patients completed at least 1 HRQoL scale at baseline: 437 (93.8%) of those in the TTFields plus temozolomide arm and 202 (88.2%) patients in temozolomide-alone arm (Figure 1). The baseline demographics of the patients who provided HRQoL data were comparable to those of the intention-to-treat population[15] and were well balanced between treatment arms in this subpopulation (Table 1).

HRQoL Completion Rates and Baseline Scores

Adherence to HRQoL assessments decreased from 91.9% at baseline to 65.8% (431 of 655 patients alive) at 3 months and dropped to 41.7% (197 of 473 patients alive) at 12 months of follow-up (Figure 1). Mean and median baseline HRQoL scores were comparable between arms for all preselected scales/items (eTable 1 in Supplement 1), as well as the exploratory scales and items. Reference values of HRQoL scores of a healthy general population[25] were available for 7 of 9 predefined scales and items (except itchy skin and weakness of legs). Patients with glioblastoma after completion of radiochemotherapy showed clinically relevant worse functioning or more symptoms compared with the general population on all scales except pain, which was similar.[25]

Mean Changes in HRQoL From Baseline and the Repeated-Measures Mixed-Effect Model

Mean changes in HRQoL over time for the global health status is presented in Figure 2A and for all 9 predefined HRQoL scales in the eFigure in Supplement 1. Throughout the 12-month assessment period, mean changes from baseline were stable (<10-point change from baseline) for all 9 predefined HRQoL scales in both treatment arms (eFigure in Supplement 1) with the exception of itchy skin (Figure 2B). For itchy skin, a clinically relevant deterioration (ie, an increase in itchy skin) compared with baseline was seen at the month 3 evaluation in the TTFields plus temozolomide arm (mean [SD] increase, 10.4 [30.1] points vs an improvement of 2.3 [24.4] points in the temozolomide arm). For differences between treatment arms, patients treated with TTFields plus temozolomide had significantly and clinically relevant worse itchy skin at 3, 6, and 9 months than patients treated with temozolomide alone, but not at 12 months (mean [SD] increase of 10.4 [30.1] in the TTFields plus temozolomide arm vs a decrease of 2.3 [24.4] in the temozolomide-alone arm, P = .005; increase of 8.1 [31.6] in the TTFields plus temozolomide arm vs a decrease of 4.2 [31.4] in the temozolomide-alone arm, P = .008; increase of 5.3 [28.0] in the TTFields plus temozolomide arm vs a decrease of 5.2 [29.6] in the temozolomide-alone arm, P = .04; increase of 4.6 [32.8] in the TTFields plus temozolomide arm vs a decrease of 1.9 [36.9] in the temozolomide-alone arm, P = .66, respectively). For all other scales, there were no statistically significant or clinically relevant differences between treatment arms.

The repeated-measures mixed-effect model supported this finding, with no statistically significant difference between treatment arms in HRQoL scores over time in any predefined scale or item except for itchy skin (P < .001), which was worse in the TTFields plus temozolomide arm (eTable 2 in Supplement 1). The sensitivity analyses showed that the results of the linear mixed model were robust.

Stable or Improved HRQoL During Progression-Free Time

Compared with baseline, more patients in the TTFields plus temozolomide arm compared with the temozolomide-alone arm reported stable or improved scores for global health status (53.5% vs 38.0%, respectively, P = .001), physical func-

Table 2. Stable or Improved Health-Related Quality of Life During Progression-Free Time

Characteristic	TTFields Plus Temozolomide (n = 361)	Temozolomide (n = 142)	P Value	α Value
Pain				
Stable/improved from baseline, No./No. (%)	205/361 (56.8)	51/142 (35.9)	<.001	.05
Median duration (95% CI), mo	6.2 (5.9 to 7.0)	6.3 (5.6 to 9.1)	.88	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 0)	0 (0 to 0)	.80	
Global health status				
Stable/improved from baseline, No./No. (%)	192/359 (53.5)	53/141 (37.6)	.001	.025
Median duration (95% CI), mo	6.3 (5.9 to 7.4)	7.9 (5.9 to 9.8)	.24	
Median CFB AUC until last stable/improved status (95% CI)	24.4 (11.9 to 35.0)	65.9 (13.1 to 121.3)	.13	
Physical functioning				
Stable/improved from baseline, No./No. (%)	195/361 (54.0)	54/142 (38.0)	.001	.017
Median duration (95% CI), mo	6.2 (5.9 to 8.2)	9.1 (5.9 to 9.8)	.21	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 18.7)	0 (0 to 30.0)	.53	
Weakness of legs				
Stable/improved from baseline, No./No. (%)	206/351 (58.7)	58/138 (42.0)	.001	.013
Median duration (95% CI), mo	6.3 (6.0 to 8.3)	9.1 (5.9 to 9.8)	.08	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 0)	0 (0 to 0)	.51	
Cognitive functioning				
Stable/improved from baseline, No./No. (%)	181/359 (50.4)	55/142 (38.7)	.02	.01
Median duration (95% CI), mo	6.0 (4.9 to 6.5)	6.2 (5.7 to 9.6)	.65	
Median CFB AUC until last stable/improved status (95% CI)	26.3 (0 to 48.6)	0 (0 to 93.3)	.37	
Emotional functioning				
Stable/improved from baseline, No./No. (%)	196/359 (54.6)	62/142 (43.7)	.03	.008
Median duration (95% CI), mo	6.3 (6.0 to 8.3)	7.7 (5.8 to 9.4)	.38	
Median CFB AUC until last stable/improved status (95% CI)	22.6 (5.8 to 35.0)	25.2 (0 to 54.4)	.73	
Social functioning				
Stable/improved from baseline, No./No. (%)	173/359 (48.2)	58/142 (40.8)	.14	.007
Median duration (95% CI), mo	6.2 (5.9 to 7.1)	6.7 (5.9 to 9.6)	.40	
Median CFB AUC until last stable/improved status (95% CI)	16.5 (0 to 47.2)	0 (0 to 54.4)	.90	
Role functioning				
Stable/improved from baseline, No./No. (%)	173/361 (47.9)	58/141 (41.1)	.17	.006
Median duration (95% CI), mo	5.9 (4.4 to 6.3)	7.3 (5.7 to 9.3)	.27	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 25.0)	46.7 (0 to 75.8)	.34	
Itchy skin				
Stable/improved from baseline, No./No. (%)	148/349 (42.4)	64/137 (46.7)	.39	.0056
Median duration (95% CI), mo	6.0 (4.7 to 6.3)	6.7 (5.6 to 9.4)	.37	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 0)	0 (−102.2 to 0)	.19	

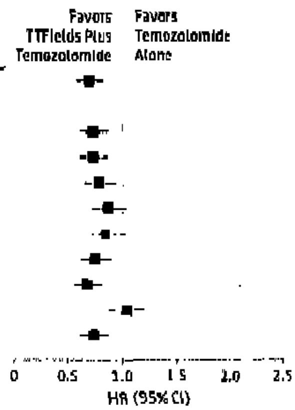
Abbreviations: AUC, area under the curve; CFB, change from baseline; TTFields, tumor-treating fields.

tioning (54.0% vs 37.0%, respectively; $P = .001$), pain (56.8% vs 35.9%, respectively; $P < .001$), and weakness of legs (58.7% vs 42.0%, respectively; $P = .001$) but not in any of the other HRQoL scales and items. However, the duration of stable or improved HRQoL was shorter in the TTFields plus temozolomide arm, although not significantly different from the temozolomide arm for any of the HRQoL scales and items. Overall, with a combination of these measures, the area under the curve analysis showed no significant differences between treatment arms for any of the HRQoL scales and items, indicating a similar HRQoL between treatment arms while patients did not experience tumor progression (Table 2).

Figure 3. Deterioration-Free Survival and Time to Deterioration

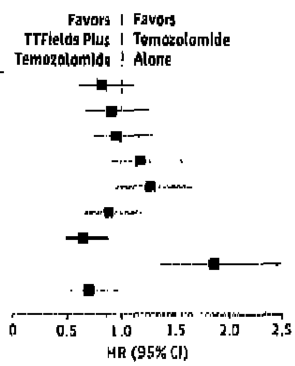
A Deterioration-free survival

Source	Median, mo TTFields Plus Temozolomide	Median, mo Temozolomide Alone	HR (95% CI)
Progression-free survival	6.7	4.0	0.69 (0.57-0.83)
Deterioration-free survival			
Global health status	4.8	3.3	0.73 (0.60-0.88)
Physical functioning	5.1	3.7	0.73 (0.60-0.88)
Cognitive functioning	4.4	3.6	0.78 (0.64-0.94)
Role functioning	4.3	3.8	0.86 (0.71-1.02)
Social functioning	4.5	3.9	0.84 (0.70-1.06)
Emotional functioning	5.3	3.9	0.75 (0.62-0.91)
Pain	5.6	3.6	0.67 (0.56-0.81)
Itchy skin	3.9	4.0	1.03 (0.85-1.25)
Weakness of legs	5.6	3.9	0.74 (0.61-0.89)



B Time to deterioration

Source	Median, mo TTFields Plus Temozolomide	Median, mo Temozolomide Alone	HR (95% CI)
Global health status	14.130	9.63	0.81 (0.60-1.10)
Physical functioning	14.170	13.97	0.90 (0.66-1.24)
Cognitive functioning	10.270	13.97	0.95 (0.71-1.28)
Role functioning	9.20	13.97	1.16 (0.86-1.56)
Social functioning	10.60	13.97	1.25 (0.91-1.72)
Emotional functioning	13.430	14.03	0.88 (0.64-1.21)
Pain	13.370	12.13	0.65 (0.48-0.89)
Itchy skin	8.167	14.40	1.85 (1.33-2.57)
Weakness of legs	14.170	14.03	0.71 (0.51-0.99)



Deterioration-free survival (A) and time to deterioration (B) for health-related quality-of-life domains in patients who received tumor-treating fields (TTFields) plus temozolomide compared with temozolomide alone. HR indicates hazard ratio.

Deterioration-Free Survival and TTD

The addition of TTFields to standard temozolomide chemotherapy resulted in statistically significant longer deterioration-free survival in global health status, physical and emotional functioning, pain, and weakness of legs (Figure 3A and eTable 2 in Supplement 1); the significant difference remained after correction for multiple testing. When progression was removed as a deterioration event (TTD), there was no negative influence of TTFields plus temozolomide treatment on the TTD of HRQoL (Figure 3B) except for itchy skin, which was worse in the TTFields plus temozolomide arm (8.2 vs 14.4 months). In contrast, the addition of TTFields to temozolomide resulted in a statistically significant prolongation until deterioration for pain (13.4 vs 12.1 months, $P < .01$). There were no other significant differences in TTD between arms (Figure 3B).

Discussion

In our detailed analysis of HRQoL during therapy with TTFields in addition to temozolomide, no significant difference was found between the groups in patients' HRQoL over time except for the skin reaction. As expected, itchy skin was reported more frequently in patients treated with TTFields because of the transducer arrays that have to be placed on the scalp of the patient. Consistently, over half of the patients also reported skin irritation as an adverse event. We had hypothesized that patients treated with TTFields may have better HRQoL in some domains as a result of active participation in the fight against cancer and the frequent interactions between patients and caregivers and device technicians regarding the device. However, on a group level, global health status and emotional functioning were not significantly different between treatment arms. Likewise, our hypotheses that the addition of TTFields would result in worse role and social functioning (due to the visibility of the device) and worse physical functioning were not confirmed. In line with our hypotheses, cognitive functioning, pain, and weakness of legs were not negatively affected by the addition of TTFields to temozolomide treatment. Most relevant for patients, HRQoL was maintained (in 8 of 9 of the predefined scales/items) over time. Combining the results of the survival and HRQoL analyses suggests that the addition of TTFields to adjuvant temozolomide is of value to patients with glioblastoma.

Patients who received TTFields had significantly longer deterioration-free survival compared with those in the temozolomide-alone arm for global health status (4.8 vs 3.3 months; $P < .01$), physical (5.1 vs 3.7 months; $P < .01$) and

emotional functioning (5.3 vs 3.9 months; $P < .01$), pain (5.6 vs 3.6 months; $P < .01$), and weakness of legs (5.6 vs 3.9 months; $P < .01$). For the other scales and items, there was no significant difference in deterioration-free survival between the 2 treatment arms. The prolonged deterioration-free survival for these scales is explained by the extended progression-free survival for patients in the combined TTFields plus temozolomide arm, as progressive disease is included as an event in this analysis. Therefore, TTD analyses, excluding progressive disease as an event, is important to illustrate the influence of a treatment on HRQoL. TTD was not significantly different across any HRQoL scale or item in TTFields-treated patients except for pain and itchy skin, indicating that treatment with TTFields had an influence only on the level of pain and itchy skin. In patients treated with TTFields, TTD was significantly longer for pain (13.4 vs 12.1 months; $P < .01$) and significantly shorter for itchy skin (8.2 vs 14.4 months; $P < .001$). The difference between deterioration-free survival and TTD indicates the importance of disease progression (rather than treatment) as a key event driving HRQoL decline, as suggested by previous studies.[26,27] Moreover, in only 1% of patients, regardless of treatment arm, was a clinically relevant improvement in HRQoL seen after initial deterioration, supporting this observation. Taken together, the results of the deterioration-free survival and TTD analyses support the results of the longitudinal analysis by showing that the addition of TTFields to the standard of care did not adversely affect HRQoL. In fact, the delay in TTD for pain seen in TTFields-treated patients may reflect a delay in the occurrence of tumor-related headaches (although not significant, patients in the TTFields plus temozolomide arm had a longer TTD compared with patients in the temozolomide-alone arm for headaches: hazard ratio, 0.77; 95% CI, 0.54-1.10; $P = .16$). Future studies are needed to better understand this finding, as the median TTD values for pain were longer than the median progression-free survival for both arms.

Limitations

A common problem in many cancer clinical trials, as in this study, is missing HRQoL data. This absence is especially apparent during the follow-up period, hampering longitudinal data analysis. Patients with better prognostic factors and a good treatment response will be overrepresented at later stages.[28,29] However, our mixed-model analyses, accounting for missing data, confirmed the results found in the mean change from baseline analyses. Another limitation of clinical trials is generalizability of results—patients in clinical trials may not be representative of a general glioblastoma population. Patients in this trial were included only if they successfully completed the combined radiochemotherapy. In addition, it may be that not all patients are prepared to accept wearing the TTFields device. Nevertheless, patients participating in this trial were similar with respect to clinical characteristics to those participating in the EORTC 26981 study[13] comparing radiotherapy alone with radiotherapy plus temozolomide. Lastly, many factors may affect HRQoL, such as age, comorbidity, tumor characteristics, previous antitumor treatment (eg, radiation dose), and supportive treatment. However, it is unlikely that these factors influenced our conclusion, as the objective of this study was to compare HRQoL results between 2 treatment arms in which patients were similar due to randomization.

Conclusions

Use of TTFields prolongs progression-free and overall survival in patients with glioblastoma. The addition of this novel device-delivered treatment neither negatively affects nor improves functioning and well-being of the patient, including critical HRQOL issues, such as role, social, and physical functioning. Patients reported more itchy skin, which is a direct and expected consequence of the placement of transducer arrays on the patients' scalp. Considering the net clinical benefit, our HRQoL data support the addition of TTFields to standard therapy in patients with glioblastoma.

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Author Contributions: Drs Taphoorn and Dirven contributed equally to the study. Drs Stupp and Kirson had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Study supervision: Bruna, Roth, Desai, Villano, Kirson, Ram, Stupp.

Conflict of Interest Disclosures: Dr Taphoorn has performed paid consultancy for Hoffmann-La Roche. Dr Lavy-Shahaf is an employee of and received personal fees from Novocure during the conduct of the study. Drs Weinberg and Kirson are employees of and own minority stock in Novocure. Dr Taillibert received fees from Centre-de-Recherche-en-Neuro-Oncologie for enrolling patients at Salpêtrière University Hospital during the conduct of the study. Dr Idbaih received research support from Foundation ARC, IntselChimos, Beta-Innov, and Carthera and travel support from Carthera and Hoffmann-La Roche and served as a paid member of the advisory boards of BMS, Hoffmann-La Roche, and Lettre du Cancérologue. Dr Hottinger received research support from Novocure and served on advisory boards of Servier and BMS (fees paid to the institution). Dr Roth served as a paid member of the advisory boards of Roche and MSD and received personal fees for lectures on behalf of BMS and Novocure. Dr Ram received grants and personal fees from and owns minority stock in Novocure. Dr Stupp received nonfinancial support from Novocure, and his institution received fees from Celgene, Novartis, AbbVie, Merck KGaA (Darmstadt), and MSD-Merck & Co. Dr Stupp's spouse is a full-time employee of Celgene. No other conflicts were reported.

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Role of the Funder/Sponsor: Novocure Ltd had a role in the design and conduct of the study; collection, management, and analysis of the data; and decision to submit the manuscript for publication. The study was designed by Drs Stupp and Ram, together with representatives from Novocure, mainly Dr Kirson. The study oversight was supported and monitored by a clinical research organization, which also held the database. Data were collected by the investigators and monitored by the clinical research organization. The statistical analysis plan for the quality of life analyses was developed by Drs Taphoorn, Dirven, Kirson, and Lavy-Shahaf, the sponsor's statistician. Data interpretation was the responsibility of Drs Taphoorn, Dirven, Kirson, and Stupp. The first draft of this manuscript was developed by Drs Taphoorn, Dirven, Kirson, and Stupp. A subsequent mature draft and prefinal version were circulated among all authors who gave additional input, contributed to, and approved the manuscript. The decision to publish the data and its interpretation was made by Drs Stupp and Ram and was supported by all coauthors.

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JAMA | Original Investigation

Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma
A Randomized Clinical Trial

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IMPORTANCE Tumor-treating fields (TTFields) is an antimitotic treatment modality that interferes with glioblastoma cell division and organelle assembly by delivering low-intensity alternating electric fields to the tumor.

OBJECTIVE To investigate whether TTFields improves progression-free and overall survival of patients with glioblastoma, a fatal disease that commonly recurs at the initial tumor site or in the central nervous system.

DESIGN, SETTING, AND PARTICIPANTS In this randomized, open-label trial, 695 patients with glioblastoma whose tumor was resected or biopsied and had completed concomitant radiochemotherapy (median time from diagnosis to randomization, 3.8 months) were enrolled at 83 centers (July 2009-2014) and followed up through December 2016. A preliminary report from this trial was published in 2015; this report describes the final analysis.

INTERVENTIONS Patients were randomized 2:1 to TTFields plus maintenance temozolomide chemotherapy ($n = 466$) or temozolomide alone ($n = 229$). The TTFields, consisting of low-intensity, 200 kHz frequency, alternating electric fields, was delivered (≥ 18 hours/d) via 4 transducer arrays on the shaved scalp and connected to a portable device. Temozolomide was administered to both groups (150-200 mg/m^2) for 5 days per 28-day cycle (6-12 cycles).

MAIN OUTCOMES AND MEASURES Progression-free survival (tested at $\alpha = .046$). The secondary end point was overall survival (tested hierarchically at $\alpha = .048$). Analyses were performed for the intent-to-treat population. Adverse events were compared by group.

RESULTS Of the 695 randomized patients (median age, 56 years; IQR, 48-63; 473 men [68%]), 637 (92%) completed the trial. Median progression-free survival from randomization was 6.7 months in the TTFields-temozolomide group and 4.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.52-0.76; $P < .001$). Median overall survival was 20.9 months in the TTFields-temozolomide group vs 16.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; $P < .001$). Systemic adverse event frequency was 48% in the TTFields-temozolomide group and 44% in the temozolomide-alone group. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of patients who received TTFields-temozolomide vs no patients who received temozolomide alone.

CONCLUSIONS AND RELEVANCE In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival. These results are consistent with the previous interim analysis.

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Glioblastoma is the most common and aggressive primary brain tumor with an annual incidence of 3.19 per 100 000.[1-3] The disease course is typically rapid, with only approximately 1 in 4 patients alive 2 years after diagnosis, and only 5% to 10% of patients alive at 5 years.[1,4-7]

Since the current standard of care was established, consisting of surgical resection or biopsy, followed by radiotherapy with concomitant temozolomide chemotherapy, followed by maintenance temozolomide for 6 to 12 months,[6] little progress has been made in the treatment of this disease.[3,8,9] Most trials have shown median progression-free survival and median overall survival from diagnosis of 6.2 to 7.5 months and 14.6 to 16.7 months, respectively.[4-6,8]

Tumor-treating fields (TTFields) are an antimitotic treatment that selectively affects dividing glioblastoma cells by delivering low-intensity, intermediate-frequency (200 kHz) alternating electric fields via transducer arrays applied to the scalp.[10,11] Tumor-treating fields cause mitotic arrest and apoptosis of rapidly dividing cells.[10,11] Preclinical studies demonstrated increased sensitivity to chemotherapy with the addition of TTFields in human glioblastoma cell lines and in animal tumor models.[12] In a randomized phase 3 trial involving 237 patients with recurrent glioblastoma whose several lines of prior therapy had failed, TTFields monotherapy was compared with the treating physicians' best choice of salvage chemotherapy. Although no survival difference was observed, the higher objective response rate (12% vs 7%) suggested single-modality activity of TTFields.[13]

In 2009, this randomized phase 3 clinical trial was initiated, comparing maintenance temozolomide alone with maintenance temozolomide in combination with TTFields among patients with glioblastoma. A preplanned interim analysis involving the first 315 patients randomized was previously reported and demonstrated improved progression-free and overall survival.[14] This article reports the final analysis involving all 695 randomized patients, with a median follow-up of 40 months and a minimum follow-up of 24 months.

Key Points

Question Does the use of tumor-treating fields (TTFields), consisting of low-intensity, alternating electric fields delivered via transducer arrays applied to the scalp, when added to maintenance temozolomide chemotherapy, improve progression-free survival for patients with glioblastoma?

Findings In this randomized clinical trial involving 695 patients with glioblastoma who had completed initial radiochemotherapy, median progression-free survival from randomization was 6.7 months in the TTFields plus temozolomide group and 4.0 months in the temozolomide-alone group (hazard ratio, 0.63), a significant difference.

Meaning Among patients with glioblastoma, the addition of TTFields to maintenance temozolomide chemotherapy resulted in statistically significant improvement in survival. These results are consistent with those reported in a previous interim analysis.

Methods

The study was approved by the institutional review boards or ethics committees of all participating centers, and all patients provided written informed consent before entering the study. The trial protocol and statistical analysis plan are included in Supplement 1.

Study Population

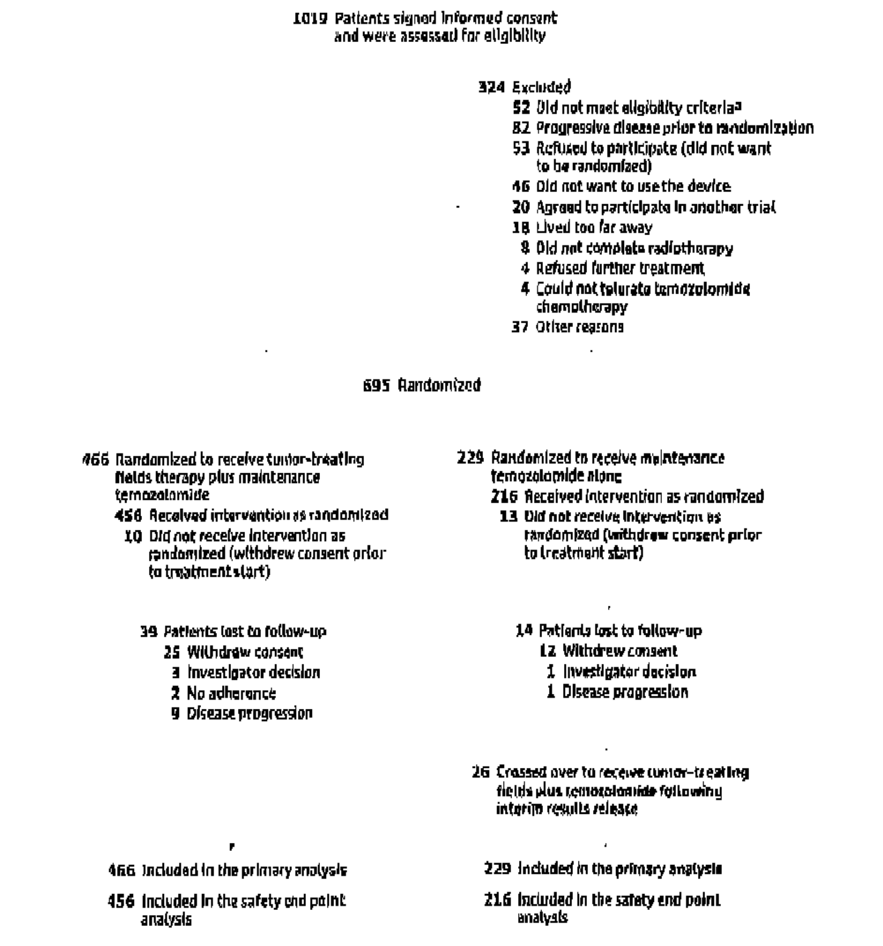
Patients eligible for this study were aged 18 years or older, had a Karnofsky performance score of 70 or higher (a score of ≥70 ensures independence in activities of daily living), and had newly diagnosed and histologically confirmed supratentorial glioblastoma (World Health Organization [WHO] grade IV astrocytoma[15]). All participants had undergone maximal safe debulking surgery when feasible or biopsy and had completed standard radiotherapy with concomitant temozolomide at the time of enrollment. Prior use of implanted carmustine wafers was allowed. Patients with evidence of progressive disease following radiochemotherapy, infratentorial tumor location, and severe comorbidities were excluded. Adequate hematological, liver, and kidney function tests to allow for temozolomide chemotherapy were required.[6,14,16]

Study Design and Treatment

This multicenter, open-label, randomized clinical phase 3 trial, recruited 695 patients at 83 sites in North America, Europe, the Republic of Korea, and Israel. The trial was designed to test the efficacy and safety of TTFields in combination with best standard of care in the treatment of newly diagnosed glioblastoma. Patients were randomized after the end of radiochemotherapy at a ratio of 2:1 to receive standard maintenance temozolomide chemotherapy (150-200 mg/m²/d for 5 days every 28 days for 6 cycles) with or without the addition of TTFields. Tumor treating fields treatment was to be initiated at least 4 weeks but not more than 7 weeks from the last day of radiotherapy. Maintenance temozolomide was delivered in 28-day cycles according to the protocol established by the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada (NCIC) Clinical Trials Group.[6] Extension of the duration of maintenance temozolomide beyond 6 cycles was allowed per local practice. Randomization was performed using a central web-based randomization system and was stratified by extent of resection (biopsy, partial resection, gross total resection) and by the methylation status of the O6-methylguanine-DNA methyltransferase (*MGMT*) gene promoter (methylated, unmethylated, unknown).

Treatment with TTFields was delivered through 4 transducer arrays with 9 insulated electrodes each placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain (Optune, Novocure Inc). Transducer array layouts were determined using a TTFields mapping software system to optimize field intensity within the treated tumor (NovoTAL, Novocure Inc). Patients were trained by the nursing staff and device technician to operate the device independently, replace transducer arrays, and troubleshoot any

Figure 1. Recruitment and Inclusion of Patients in the Study



[a] Ten patients were out of randomization window; 8 had low platelet counts; 17, infratentorial disease; 4, elevated liver enzymes; 3, programmable shunts; 10, pacemakers or defibrillators.

alarm conditions (eg, disconnected cables). All treatment was delivered on an outpatient basis and at home. The transducer arrays were supplied in individual sterile packages, and replaced by the patient, a caregiver, or a device technician twice a week. Although uninterrupted treatment was recommended, the patient could take short treatment breaks to tend to personal needs. The patient was advised to continue treatment for no fewer than 18 hours a day.

If tumor progression occurred, second-line therapy was offered per local practice. However, in the experimental group, TTFields could be continued until second radiologic progression occurred or for a maximum of 24 months.

Patient Surveillance and Follow-up

Patients diagnosed with glioblastoma who had undergone surgical resection or biopsy and had received standard radiochemotherapy were randomized to receive either TTFields plus temozolomide or temozolomide alone between July 2009 and December 2014 (Figure 1). The database was locked for final analysis on December 28, 2016. Baseline contrast-enhanced magnetic resonance imaging (MRI) of the brain was required within 2 weeks before starting treatment with maintenance temozolomide with or without TTFields. A complete physical examination and laboratory parameters were performed within 1 week of treatment start. Evaluation also included the EORTC QLQ-C30 quality-of-life questionnaire with its brain-specific module (BN-20)[17,18] and a Mini-Mental State Examination (a test result of 27-30 points is considered normal function). Patients were seen monthly for medical follow-up and routine laboratory examinations. Quality of life was assessed every 3 months.

Adverse events were recorded for 2 months after treatment discontinuation according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) v3.0. Adverse events were presented descriptively as number and percentage of patients with each adverse event term for all patients available at the time of the analysis.

Independent Radiological Review

Magnetic resonance imaging was performed at 2-month intervals until second progression. In the event of clinical progression, MRI was to be performed within 1 week after the investigator had become aware of it. All MRIs were reviewed by 2 blinded central independent radiologists (BioClinica Inc) and were evaluated for tumor response and progression (Macdonald criteria[19]). For cases

in which the 2 reviewers were not in agreement, a third blinded radiologist adjudicated between them.

Central *MGMT* Testing, Pathology Review, and Molecular Analyses

In patients with paraffin-embedded tumor tissue available, evaluation of the *MGMT* methylation status was performed using quantitative methylation-specific polymerase chain reaction[3,30] by a central laboratory licensed by MDxHealth. If the *MGMT* methylation status could not be determined centrally prior to randomization, local *MGMT* methylation status was used for stratification. All data analyses were based on the central blinded assessment.

Patients were included based on initial local histological diagnosis. A retrospective pathology review and evaluation of molecular testing was performed by a neuropathologist (B.L.) and molecular biologist (M.E.H.). Deletion of chromosomal arms 1p and 19q and amplification of the epidermal growth factor receptor (*EGFR*) were evaluated by fluorescent in situ hybridization (FISH), immunohistochemistry (IHC), or both; and the mutation status of the isocitrate dehydrogenase 1 (*IDH1*) gene was determined by immunohistochemistry for the most common mutant *IDH1-R132H* as described previously.[31] For cases in which insufficient tissue was available for *EGFR* FISH, the result of *EGFR* IHC was used as a surrogate (Hirsch score, ≥200 amplified; <200, not amplified).[32]

Outcomes

Primary and Secondary End Points

The primary end point was progression-free survival, and the secondary end point was overall survival, with analyses conducted in the intent-to-treat population.

The protocol defined that overall survival would be analyzed in a per-protocol population including only patients who received their original allocated treatments. However, 26 patients (11%) in the temozolomide-alone control group crossed over and received TTFields after December 2014, following release of the results of the interim analysis of the trial. These 26 patients had more favorable baseline characteristics than the rest of the control patients (*MGMT* methylated, 48%; Karnofsky performance score, 80-100; time from end of radiotherapy to randomization, 31 days) and received more cycles of temozolomide (median, 10.5 cycles). To avoid possible bias, these patients were analyzed as randomized in the control group according to the intent-to-treat principle.

Exploratory End Points

Other predefined exploratory end points were percentage of patients alive and progression free at 6 months, annualized survival rates, quality of life, Mini-Mental State Examination, and Karnofsky performance score. The quality-of-life data are not reported in this article.

Statistical Analysis

Primary and Secondary End Points

For the primary end point of progression-free survival, the calculated sample size was 700 patients aimed to detect a hazard ratio (HR) of 0.78 or less, with 80% power allowing for 10% loss to follow-up and a 2-sided $\alpha = .05$. Overall survival was a powered secondary end point in the study (80% power; HR, 0.76; 2-sided $\alpha = .05$). To avoid multiplicity, overall survival was to be tested statistically only if the primary end point of the study was met.

To allow for 2 analyses in the trial, the final type I error of 0.05 was split between the interim and final analyses based on a standard α spending function (Lan and DeMets[33,34]). The primary end point at the final analysis would be achieved if progression-free survival was significantly longer in the TTFields plus temozolomide group using a stratified log-rank test (stratified by the randomization strata) with an α of .046 (an α of 0.014 was spent on the interim analysis).

The secondary end point would be achieved at the final analysis if overall survival was significantly longer in the TTFields plus temozolomide group using a stratified log-rank test with an α of .048 (an α of .006 was spent on the interim analysis).

Missing Data

For the analysis of progression-free survival patients were censored for progression when treatment was changed before evidence of progression (at the date of treatment change), at the date of their last MRI if lost to follow up, or upon reaching the cutoff date without progression. For the analysis of overall survival, patients without a known date of death were censored at the last known date they were documented to be alive.

Exploratory End Points

The exploratory end points of annual survival rates and the rate of progression-free survival at 6 months were compared between groups using a 1-sided *Z* distribution of the Kaplan-Meier estimates of the survival rates at the defined time point. In addition, the Cox proportional hazards model was used to analyze both progression-free survival and overall survival controlling for treatment group, age, sex, *MGMT* methylation status (as determined by the central laboratory), tumor location in the brain, and country of residence (United States vs all other countries). The threshold for significant interactions in the model was specified at an α of .05.

Post Hoc Analysis

Post hoc analyses of prespecified subgroups (*MGMT* promoter methylation status, extent of resection (complete, partial resection, or biopsy), age (continuous), performance status (90-100 vs ≤80), sex, and geographic region (United States vs the rest of the world) was performed using a multivariate analysis testing the difference between treatment groups while controlling for the other prognostic factors.

Analysis of Adverse Events and Tolerability

Differences in the incidence of adverse events between groups was tested using a χ^2 test at an α of .05. The incidence of adverse events was also compared between groups after normalizing the incidence to the average treatment duration per group. Differences in the time to decline in Karnofsky performance score and Mini-Mental State Examination were tested using a log-rank test at an α of .05. All analyses were performed using SAS version 9.4.

Table 1. Patient and Treatment Characteristics

Characteristics	No. (%) of Patients: TTFields + Temozolomide (n = 466)	No. (%) of Patients: Temozolomide Alone (n = 229)
Age, y		
Median (range)	56.0 (19-83)	57.0 (19-80)
≥65	89 (19)	45 (20)
<65	377 (81)	184 (80)
Karnofsky performance score[a]		
Median (range)	90.0 (60-100)	90.0 (70-100)
90-100	308 (66)	149 (65)
≤80	154 (33)	74 (32)
Missing	4 (1)	6 (3)
Sex		
Men	316 (68)	157 (69)
Women	150 (32)	72 (31)
Region		
United States	221 (47)	118 (52)
Outside the United States	245 (53)	111 (48)
Race/ethnicity		
White	416 (89)	201 (88)
African American	3 (1)	1 (<1)
Asian	27 (6)	19 (8)
Hispanic	18 (4)	7 (3)
American Indian	1 (<1)	1 (<1)
Antiepileptic drug use at baseline	205 (44)	95 (41)
Corticosteroid use at baseline	135 (29)	64 (28)
Mini-Mental State Examination score[b]		
27-30	356 (76)	160 (70)
≤26	88 (19)	48 (21)
Missing	22 (5)	21 (9)
Extent of resection		
Biopsy	60 (13)	29 (13)
Partial resection	157 (34)	77 (33)
Gross total resection	249 (53)	123 (54)
MGMT promotor region methylation status		
Tissue available and tested	386 (83)	185 (81)
Methylated	137 (36)	77 (42)
Unmethylated	209 (54)	95 (51)
Invalid	40 (10)	13 (7)
Slides available for central pathology review	296 (64)	138 (60)
Confirmed glioblastoma	285 (96)	134 (97)
WHO grade II or III glioma	4 (1)	2 (1)
Insufficient quality for diagnosis	7 (2)	2 (1)
IDH1-R132H status		
Tissue available and tested	260 (56)	119 (52)
Mutated	19 (7)	6 (5)
Negative test results	240 (92)	113 (95)
Invalid	1 (<1)	
EGFR status		
Tissue available and tested	252 (54)	112 (49)
Amplified	102 (41)	43 (38)
Not amplified	147 (58)	68 (61)
Invalid	3 (1)	1 (1)
Tumor tissue chromosomes 1p and 19q		
Tissue available and tested	259 (56)	112 (49)
Codeletion	2 (1)	
Loss 1p only	4 (2)	1 (1)
Loss 19q only	3 (1)	3 (3)
Retained	239 (92)	102 (91)
Invalid	11 (4)	6 (5)

(continued)

Table 1. Patient and Treatment Characteristics (continued)

Characteristics	No. (%) of Patients: TTFields + Temozolomide (n = 466)	No. (%) of Patients: Temozolomide Alone (n = 229)
Tumor position[c]		
Corpus callosum	25 (5)	12 (5)
Frontal lobe	190 (41)	84 (37)
Occipital lobe	58 (12)	27 (12)
Parietal lobe	146 (31)	89 (39)
Temporal lobe	191 (41)	90 (40)
Missing	3 (1)	3 (1)
Tumor location[c]		
Left hemisphere	214 (46)	99 (43)
Right hemisphere	249 (53)	127 (55)
Both hemispheres	4 (1)	2 (1)
Corpus callosum	15 (3)	9 (4)
Missing	1 (<1)	1 (<1)
Treatment delivery		
Completed standard radiation therapy		
57-63 Gy	422 (91)	212 (93)
<57 Gy	21 (5)	11 (5)
>63 Gy	18 (4)	3 (1)
Dose not reported	5 (1)	3 (1)
Concomitant radiation therapy and temozolomide		
Yes	433 (93)	212 (93)
No record available	33 (7)	17 (7)
Time from last day of radiation treatment to randomization, median (range), d	37 (15-128)	36 (15-70)
Time from initial diagnosis to randomization, median (range), mo	3.8 (1.7-6.2)	3.7 (1.4-6.3)
Temozolomide cycles, median (range)	6 (0-51)	5 (0-33)
Tumor-treating fields therapy		
Duration, median (range), mo	8.2 (0-82)	
≥18 h/d (first 3 mo of treatment), mean	347 (75)	

Abbreviations: *EGFR*, epidermal growth factor receptor gene; *IDH1*-R132H, isocitrate dehydrogenase 1 (*IDH1*) R132H mutation site; *MGMT*, O^6-methylguanine-DNA-methyltransferase gene; TTFields, tumor-treating fields; WHO, World Health Organization.

[a] Karnofsky performance score ranges from 0 to 100 in 10-point increments, with a higher score representing better performance status.

[b] Scores range from 1 to 30, with a higher score representing better cognitive function.

[c] Multiple positions for each patient allowed (for multifocal tumors).

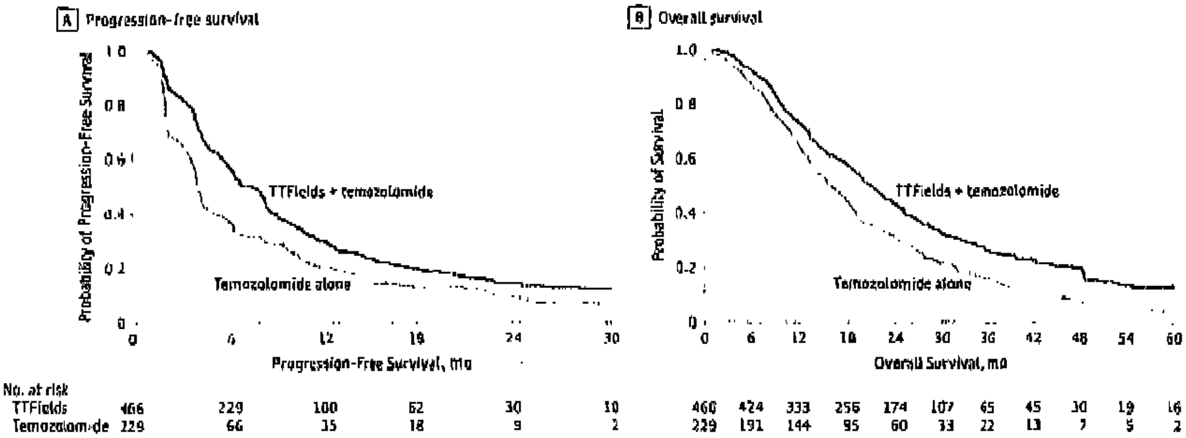
Results

Study Participants

Four hundred and sixty-six patients were randomized to receive TTFields plus temozolomide and 229 to receive temozolomide alone (Figure 1). Patient baseline characteristics were balanced between the 2 groups (Table 1). The median age was 56 years (interquartile range [IQR], 48-63 years), 68% were men, and median Karnofsky performance score was 90%. Eighty-nine percent of patients were white, and 49% of the patients were treated in the United States.

Fifty-four percent had undergone a gross total resection (>95% of the tumor removed; as assessed and reported by the surgeon), 13% of patients had a diagnostic biopsy only. Histological slides for central pathology review were available for

Figure 2. Kaplan-Meier Survival Curves for Patients Included in the Final Analysis in the Intent-to-Treat Population



A, Median progression-free survival from randomization for the tumor-treating fields (TTFields) plus temozolomide group was 6.7 months and was 4.0 months for the temozolomide-alone group (hazard ratio [HR], 0.63; 95% CI, 0.52-0.76; $P < .001$). B, Median survival from randomization was 20.9 for the TTFields plus temozolomide group vs 16.0 months for the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; $P < .001$). Median follow up was 44 months (range, 25-91 months) in both groups.

434 of 695 patients (62%). The local diagnosis of glioblastoma was confirmed in 419 of 434 patients (97%). For 6 cases WHO grade II or III diagnoses were made, and for the remaining 9 patients, the available tissue for review did not allow for a definitive diagnosis or showed no tumor, yet all these patients were included in the intent-to-treat analysis. Tumor tissue for *MGMT* testing was available for 82% of the patients; of the cases with a valid test (518 of 571) 41% were *MGMT* methylated (40% TTFields plus temozolomide group and 45% for the temozolomide-only group). In 7% of tumors, expression of the *IDH1*-R132H mutant was demonstrated by a positive immunohistochemistry, *EGFR* was amplified in 40%.

Tumor location (lobe, hemisphere) in the brain was also comparable between the groups. The median time from histological diagnosis to randomization was 3.8 months (range, 1.7-6.2 months) for patients in the TTFields plus temozolomide group, and 3.7 months (range, 1.4-6.3 months) for those in the temozolomide-only group. Median time from the end of radiotherapy to randomization was 37 days in the TTFields plus temozolomide group and 36 days in the temozolomide-only group and occurred in most patients after starting of the first cycle of maintenance temozolomide. Median time from randomization to TTFields was 5 days (IQR, 3-7 days).

Treatment Delivery

All patients had completed radiotherapy and concomitant temozolomide as per local practice. The median number of temozolomide cycles until first tumor progression was 6 (range, 0-51) for the TTFields plus temozolomide group and 5 (range, 0-33) for the temozolomide-only group; the median duration of TTFields treatment was 8.2 months (range, 0-82 months), 51% (n = 237) of patients continued TTFields after the first progression.

Efficacy End points

After a median follow-up of 40 months (IQR, 34-66 months), and a minimum follow-up of 24 months, the primary end point of median progression-free survival was 6.7 months (95% CI, 6.1-8.1 months) for patients treated with TTFields plus temozolomide vs 4.0 months (95% CI, 3.8-4.4 months) for patients treated with temozolomide alone, for a proportional hazard ratio (HR) of 0.63 (95% CI, 0.52-0.76; $P < .001$; stratified log-rank test; Figure 2A). For the secondary end point of overall survival, the median survival duration from randomization was 20.9 months (95% CI, 19.3-22.7 months) in the TTFields plus temozolomide group vs 16.0 months (95% CI, 14.0-18.4 months) in the temozolomide-only group, proportional HR of 0.63 (95% CI, 0.53-0.76; $P < .001$; stratified log-rank test; Figure 2B).

In exploratory analyses, the percentage of patients alive at 2 years from randomization was 43% (95% CI, 39%-48%); at 3 years, 26% (95% CI, 22%-31%), and at 5 years, 13% (95% CI, 9%-18%) in the TTFields plus temozolomide group and for the temozolomide-only group at 2 years was 31% (95% CI, 25%-38%; $P < .001$); at 3 years, 16% (95% CI, 12%-23%; $P = .009$); and at 5 years, 5% (95% CI, 2%-11%; $P = .004$). Progression-free survival at 6 months was 56% (95% CI, 51%-61%) for patients treated with TTFields plus temozolomide and 37% (95% CI, 30%-44%) with temozolomide only ($P < .001$) (Table 2).

An exploratory Cox proportional hazards model adjusting for Karnofsky performance score, *MGMT* promotor methylation status, geographic region, age, tumor location, and extent of resection were consistent with the findings of the progression-free and overall survival analyses. The following factors were associated with longer overall survival: TTFields plus temozolomide treatment (HR, 0.63; 95% CI, 0.53-0.76; $P < .001$), female sex (HR, 0.76, 95% CI, 0.63-0.92; $P = .005$), methylated *MGMT* promoter (HR, 0.50; 95% CI, 0.41-0.62; $P < .001$), younger age (as a continuous variable; HR, 0.978 per year; 95% CI, 0.969-0.985; $P < .001$) and higher Karnofsky performance score (as a categorical variable in 10 point increments; $P < .001$). Patients with frontal tumors had nonsignificantly longer survival (HR = 0.82, CI 0.67-1.01, $P = .061$). Country of treatment and extent of resection were not

Table 2. Summary of Study End Points[a]

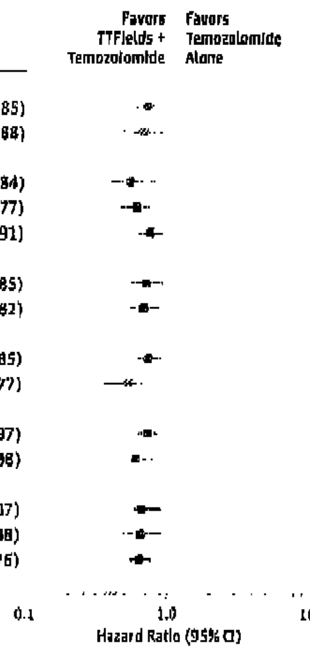
	TTFields + Temozolomide (n = 466)	Temozolomide Alone (n = 229)	Between-Group Differences
Progression-free survival			
Primary end point, median (95% CI), mo	6.7 (6.1-8.1)	4.0 (3.8-4.4)	2.7 (2.1-4.2)
Overall survival			
Secondary end point, median (95% CI), mo	20.9 (19.3-22.7)	16.0 (14.0-18.4)	4.9 (2.3-7.9)
Exploratory end points, % (95% CI			
Progression-free 6-mo survival rate	56 (51-61)	37 (30-44)	19 (15-23)
Annual survival rates, y			
1	73 (69-77)	65 (59-72)	18 (10-25)
2	43 (39-48)	31 (25-38)	12 (4-18)
3	26 (22-31)	16 (12-23)	10 (3-17)
4	20 (16-25)	8 (4-14)	12 (5-19)
5	13 (9-18)	5 (2-11)	8 (2-14)

Abbreviation: TTFields, tumor-treating fields.

[a] Survival rates are actuarial estimates according to the Kaplan-Meier method.

Figure 3. Overall Survival for Each Prognostic Patient Subgroup of Patients Treated With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone

Subgroup	TTFields + Temozolomide: No. of Patients	TTFields + Temozolomide: No. (%) Alive at End of Study	Temozolomide Alone: No. of Patients	Temozolomide Alone: No. (%) Alive at End of Study	Median Survival (IQR), mo: TTFields + Temozolomide	Median Survival (IQR), mo: Temozolomide Alone	Hazard Ratio (95% CI)
MGMT promoter region methylation status							
Unmethylated	209	18 (9)	95	3 (3)	16.9 (9.7-28.2)	14.7 (9.8-24.0)	0.66 (0.49-0.85)
Methylated	137	26 (19)	77	9 (12)	31.6 (21.1-48.5)	21.2 (12.3-37.9)	0.62 (0.44-0.88)
Resection							
Biopsy	60	5 (8)	29	0 (0)	16.5 (9.0-24.7)	11.6 (7.1-18.1)	0.50 (0.30-0.84)
Partial	157	20 (13)	77	3 (4)	21.4 (9.9-37.6)	15.1 (7.8-23.3)	0.56 (0.41-0.77)
Gross total	249	32 (13)	123	13 (11)	22.6 (13.4-39.8)	18.5 (12.1-31.6)	0.70 (0.54-0.91)
Region							
Outside United States	245	32 (13)	111	9 (8)	20.1 (11.3-32.2)	15.5 (9.3-25.6)	0.66 (0.51-0.85)
United States	221	25 (11)	118	7 (6)	22.0 (11.3-48.2)	17.1 (9.0-29.2)	0.63 (0.49-0.82)
Age, y							
<65	377	47 (12)	184	14 (8)	21.6 (12.0-39.4)	17.3 (10.6-29.3)	0.69 (0.57-0.85)
≥65	89	10 (11)	45	2 (4)	17.4 (9.0-31.5)	13.7 (7.6-24.8)	0.51 (0.33-0.77)
Karnofsky performance score							
90-100	308	39 (13)	149	11 (7)	23.3 (13.5-41.9)	17.8 (11.9-29.3)	0.70 (0.56-0.87)
≤80	154	16 (10)	74	5 (7)	14.9 (8.4-29.8)	11.0 (5.7-23.3)	0.58 (0.45-0.88)
Sex							
Women	150	21 (14)	72	6 (8)	24.6 (14.4-48.2)	18.5 (11.3-27.6)	0.64 (0.56-0.07)
Men	316	36 (11)	157	10 (6)	19.1 (10.0-34.1)	15.5 (8.4-26.5)	0.63 (0.45-0.88)
Overall	466	57 (12)	229	16 (7)	20.9 (11.3-37.6)	16.0 (9.3-27.5)	0.63 (0.53-0.76)



Data points represent Cox hazard ratios of overall survival in each subgroup of patients treated with tumor-treating fields (TTFields) plus temozolomide compared with temozolomide alone and were adjusted for the other subgroups. Error bars represent 95% CIs of the hazard ratios. The Karnofsky performance score is measured from 0 to 100 in 10-point increments, with higher scores indicating better the patient performance status.

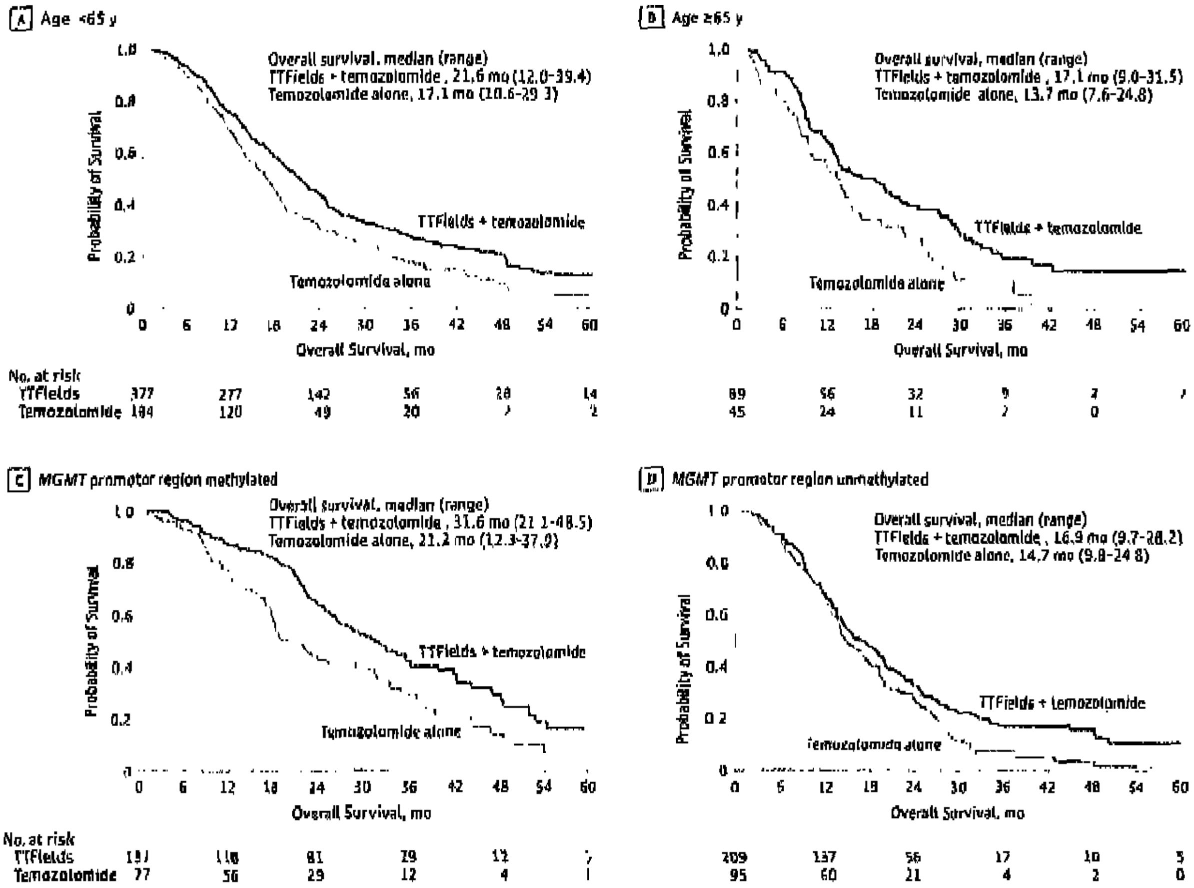
IQR, indicates interquartile range; *MGMT*, O[6]-methylguanine-DNA methyltransferase promotor region methylation status.

associated with a significant difference in survival (P = .101 and P = .183, respectively).

Post Hoc Subgroup Analysis

In post hoc analyses, TTFields plus temozolomide was associated with an increase in progression-free survival and overall survival (Figure 3; Cox proportional hazards, P < .05 for the treatment effect within each subgroup) in all subgroups of patients regardless of age, sex, Karnofsky performance score, *MGMT* promoter methylation status, geographic region, or extent of resection. Patients 65 years or older had shorter survival than patients younger than 65 years. In both age groups, TTFields plus temozolomide was associated with significantly increased survival compared with temozolomide alone for older (HR, 0.51; 95% CI, 0.33-0.77) and younger patients (HR, 0.67; 95% CI, 0.55-0.82; Figure 4A and Figure 4B).

Figure 4. Overall Survival by Patient Age and by *MGMT* Promotor Region Methylation Status



A, In comparing tumor-treating fields (TTFields) plus temozolomide vs temozolomide alone among patients younger than 65 years the hazard ratio (HR) was 0.67 (95% CI, 0.55-0.82). B, In comparing the 2 treatments among patients 65 years or older, the HR was 0.51 (95% CI, 0.22-0.77). C, In comparing the treatments among patients with O^6-methylguanine-DNA methyltransferase *MGMT* promotor region methylation, the HR was 0.62 (95% CI, 0.43-0.88). D, In comparing the treatments among patients without the *MGMT* promotor region methylation, the HR was 0.66 (95% CI, 0.49-0.85). The median follow-up of patients was 44 months (range, 25-91 months) in all groups.

Patients with tumors that lacked *MGMT* promoter methylation had a significantly shorter survival than patients with tumors with *MGMT* promoter methylation, although use of TTFields with temozolomide was associated with longer survival (HR, 0.66; 95% CI, 0.49-0.85 both in patients with tumors that were *MGMT* methylated and tumors that were unmethylated, respectively; Figure 4C and Figure 4D). In the TTFields plus temozolomide group, 265 patients who were treated with TTFields for 18 hours a day or more (monthly average in the first 6 months of treatment) had longer survival than 185 patients treated less than 18 hours a day (22.6 months, 95% CI, 19.7-25.1 months vs 19.1 months, 95% CI, 16.5-21.9; HR, 0.65; 95% CI, 0.49-0.85; *P* = .009).

Adverse Events and Tolerability

The addition of TTFields to temozolomide therapy was not associated with any significant increase in rates of systemic adverse events compared with temozolomide therapy alone (48% vs 44%, respectively; *P* = .58; Table 3), and the overall incidence, distribution, and severity of adverse events were not statistically different in patients in the 2 treatment groups. The numerically higher incidence of some adverse events in the TTFields plus temozolomide group was a reflection of the longer duration of temozolomide treatment in this group due to delayed occurrence of progression. When adverse event incidence normalized to duration of treatment was analyzed, these differences disappeared. The only exception was a higher incidence of localized skin toxic effects (medical device site reaction beneath the transducer arrays) in patients treated with TTFields plus temozolomide; mild to moderate skin irritation was observed in 52% of patients, and severe (grade 3) skin involvement occurred in 2%. Anxiety, confusion, insomnia, and headaches which were reported more frequently (statistically nonsignificant) in patients treated with TTFields at the interim analysis were not seen in the final adverse event analysis of the trial. The incidence of seizures was identical in the 2 groups.

To estimate tolerability, prespecified exploratory analyses of the association of TTFields device use with patients'

Table 3. Adverse Events by Body System and Severity (≥5% Incidence in Any Group)

	Grade 3-4 Events, No. (%) of Patients	
	TTFields + Temozolomide (n = 456)	Temozolomide Alone (n = 229)
≥1 Adverse event	218 (48)	94 (44)
Blood and lymphatic system disorders[a]	59 (13)	23 (11)
Thrombocytopenia	39 (9)	11 (5)
Gastrointestinal disorders	23 (5)	8 (4)
Asthenia, fatigue, and gait disturbance	42 (9)	13 (6)
Infections	32 (7)	10 (5)
Injury, poisoning, and procedural complications (falls and medical device site reaction)	24 (5)	7 (3)
Metabolism and nutrition disorders (anorexia, dehydration, and hyperglycemia)	16 (4)	10 (5)
Musculoskeletal and connective tissue disorders	21 (5)	9 (4)
Nervous system disorders	109 (24)	43 (20)
Seizures	26 (6)	13 (6)
Respiratory, thoracic and mediastinal disorders (pulmonary embolism, dyspnea, and aspiration pneumonia)	24 (5)	11 (5)

Abbreviation: TTFields, tumor-treating fields.

[a] The numerically slightly higher incidence of hematological toxicity, fatigue, and some other adverse effects are due to the longer treatment duration and observation time in the experimental group. The differences disappear when data are normalized to treatment duration.

activities of daily life and cognition were performed using the Karnofsky performance score and the Mini-Mental State Examination. Time to a sustained 6-point decline in the Mini-Mental State Examination score was significantly longer in the TTFields plus temozolomide group than the temozolomide-alone group (16.7 months, 95% CI, 14.7-19.0 months vs 14.2 months, 95% CI, 12.7-17.0 months, respectively; HR, 0.79; 95% CI, 0.66-0.95; $P = .01$). Time to a sustained 10-point decrease in Karnofsky performance score was also significantly longer in the TTFields plus temozolomide group than in the temozolomide-alone group (5.5 months;, 95% CI, 5.0-6.3 months vs 3.9 months; 95% CI, 3.1-5.2 months, respectively; HR, 0.80; 95% CI, 0.67-0.95; $P = .009$).

Discussion

In the final analysis of this randomized phase 3 trial, the addition of the TTFields treatment to standard temozolomide maintenance therapy, compared with standard temozolomide maintenance therapy alone, resulted in increased progression-free survival and overall survival in patients with newly diagnosed glioblastoma. After a median follow-up of 40 months, the addition of TTFields to temozolomide, compared with temozolomide alone, resulted in longer median progression-free survival from the time of randomization, 6.7 months vs 4.0 months and longer median overall survival from randomization, 20.9 months vs 16.0 months, respectively. These findings are consistent with the preliminary results reported based on a planned interim analysis of the first 315 patients enrolled, after a median follow-up of 38 months, in which median progression-free survival in the intent-to-treat population was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group (210 patients analyzed) and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide-alone group (105 patients analyzed).

In the current study, exploratory end points were consistent with the primary and secondary end points in this trial. In a post hoc analysis the effect of TTFields was observed in all clinical and molecular subgroups, including patients older than age 65 years and patients with *MGMT* unmethylated tumors.

To assess whether the improved outcome may have been related to other factors than the TTFields therapy the data were scrutinized for possible imbalances, unexpected poor performance of the control group, or differences in supportive care administered to patients between the 2 groups. Both clinical factors and molecular tumor characteristics were well balanced and comparable between the 2 groups. *MGMT* promoter methylation, the strongest predictive factor for outcome in temozolomide-treated patients,[25] was more prevalent in the control group (45% vs 40% of samples with a valid result). Patients with early tumor progression occurring during the first 3 months after diagnosis were not included in this trial, and so the randomized patient population had a better prognosis, for both groups, compared with other trials that had randomized patients before radiation therapy. The reported survival times were measured from randomization, not from diagnosis, so for an estimation of the overall outcome 3.8 months should be added in both groups. The RTOG 0525/Intergroup study, which evaluated dose-dense temozolomide, also randomized patients only after completion of radiochemotherapy.[8] Outcome of the control group in the current study and of the RTOG study were very similar, and in both studies, the median survival from randomization was 16 months.

In this trial, the rates of systemic adverse effects were not significantly different in the 2 treatment groups. The occurrence of mild to moderate skin irritation related to reaction beneath the transducer arrays of the device occurred in more than half of patients in the TTFields plus temozolomide group.

These findings are in contrast to the more than 23 randomized trials conducted over the last decade that have evaluated novel agents or intensified treatment strategies

(eg, dose-dense temozolomide, cilengitide, nimotuzumab, bevacizumab, and rindopepimut[3,5,8,26]) for treatment of patients with newly diagnosed glioblastoma and have failed to demonstrate improved survival. Innovative treatments for glioblastoma are needed.

Limitations

This study has several limitations. First, the current trial was open-label because it was considered practically unfeasible (heat and easy measure of current associated with TTFields) and ethically unacceptable to expose patients to a sham device. Although a placebo effect may affect subjective end points like quality of life or even progression-free survival by influencing the frequency of imaging and its interpretation, in the current trial a consistent benefit was observed in progression-free survival as assessed by blinded central radiology review, as well as in the gold standard of objective outcome, overall survival. Second, delivery of TTFields therapy requires the patient to continuously carry a device on a shaved scalp and may create burdens for patients. Nevertheless, the majority of patients were able to handle the device independently or with some help from a caregiver. The fact that 75% of patients achieved treatment adherence of 75% or more (ie, using the device for ≥18 hours per day) indicated good tolerability. The effects of the TTFields treatment and the need for continuous use of the device on quality of life will be reported separately.

Conclusions

In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival. These results are consistent with the previous interim analysis.

ARTICLE INFORMATION

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Acquisition, analysis, or interpretation of data: Stupp, Taillibert, Kanner, Read, Steinberg, Lhermitte, Toms, Idbaih, Ahluwalia, Fink, DiMeco, Lieberman, Zhu, Stragliotto, Tran, Brem, Hottinger, Kirson, Lavy-Shahaf, Weinberg, Kim, Paek, Nicholas, Bruna, Hirte, Weller, Hegi, Ram.
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IMPORTANCE Glioblastoma is the most devastating primary malignancy of the central nervous system in adults. Most patients die within 1 to 2 years of diagnosis. Tumor-treating fields (TTFields) are a locoregionally delivered antimitotic treatment that interferes with cell division and organelle assembly.

OBJECTIVE To evaluate the efficacy and safety of TTFields used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with glioblastoma.

DESIGN, SETTING, AND PARTICIPANTS After completion of chemoradiotherapy, patients with glioblastoma were randomized (2:1) to receive maintenance treatment with either TTFields plus temozolomide (n = 466) or temozolomide alone (n = 229) (median time from diagnosis to randomization, 3.8 months in both groups). The study enrolled 695 of the planned 700 patients between July 2009 and November 2014 at 83 centers in the United States, Canada, Europe, Israel, and South Korea. The trial was terminated based on the results of this planned interim analysis.

INTERVENTIONS Treatment with TTFields was delivered continuously (>18 hours/day) via 4 transducer arrays placed on the shaved scalp and connected to a portable medical device. Temozolomide (150-200 mg/m^2/d) was given for 5 days of each 28-day cycle.

MAIN OUTCOMES AND MEASURES The primary end point was progression-free survival in the intent-to-treat population (significance threshold of .01) with overall survival in the per-protocol population (n = 280) as a powered secondary end point (significance threshold of .006). This prespecified interim analysis was to be conducted on the first 315 patients after at least 18 months of follow-up.

RESULTS The interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 randomized to temozolomide alone, and was conducted at a median follow-up of 38 months (range, 18-60 months). Median progression-free survival in the intent-to-treat population was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (hazard ratio [HR], 0.62 [98.7% CI, 0.43-0.89]; *P* = .001). Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFields plus temozolomide group (n = 196) and 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group (n = 84) (HR, 0.64 [99.4% CI, 0.42-0.98]; *P* = .004).

CONCLUSIONS AND RELEVANCE In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

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Glioblastoma is the most devastating primary malignancy of the central nervous system in adults. Standard treatment consists of maximal safe surgical resection or a diagnostic biopsy, followed by radiotherapy (60 Gy) with concomitant daily temozolomide chemotherapy, and then maintenance treatment with temozolomide for 6 to 12 months.[1] However, most patients will die within 1 to 2 years. Median progression-free survival from diagnosis of 6.2 to 7.5 months and median overall survival from diagnosis of 14.6 to 16.7 months have been reported in clinical trials.[1-4] The reported 2- and 5-year survival rates[5] are 27% and 10%, respectively. During the last decade, all attempts to improve the outcome for patients with glioblastoma have failed when evaluated in large randomized trials.[2-4,6,7]

Tumor-treating fields (TTFields) are an antimitotic treatment that selectively disrupts the division of cells by delivering low-intensity, intermediate-frequency (200 kHz) alternating electric fields via transducer arrays applied to the shaved scalp.[8-10] In preclinical models, TTFields have been shown to cause mitotic arrest and apoptosis by disrupting mitotic spindle formation during metaphase and causing dielectrophoretic movement of polar molecules during cytokinesis.[8,10-12] In a randomized phase 3 trial in which TTFields were compared with chemotherapy in 237 patients with recurrent glioblastoma, the use of TTFields did not prolong progression-free survival or overall survival, but the therapy was associated with better quality of life without the typical chemotherapy-associated toxic effects.[13]

Based on preclinical data demonstrating a synergistic antitumor effect with chemotherapy and TTFields, and pilot clinical feasibility data in combination with temozolomide,[9] we initiated this phase 3 trial. The objective was to evaluate the efficacy and safety of TTFields used in combination with maintenance temozolomide in patients with glioblastoma after initial treatment with temozolomide and radiotherapy.

Methods

Study Population

Patients eligible for this study (1) had histologically confirmed supratentorial glioblastoma (World Health Organization grade IV astrocytoma[14]), (2) were progression-free after having undergone maximal safe debulking surgery when feasible or biopsy, and (3) had completed standard concomitant chemoradiotherapy with temozolomide. Other eligibility criteria were (1) age of 18 years or older, (2) Karnofsky Performance Status (KPS) score of 70% or higher (the KPS score describes the general condition of a patient; a KPS score ≥70% ensures some independence in activities of daily living), and (3) adequate bone marrow, liver, and renal function.

Prior use of implanted carmustine wafers was allowed. Patients with infratentorial tumor location and severe comorbidities were excluded. All patients provided written informed consent before entering the study; the study was approved by the institutional review boards or ethics committees of all 83 participating centers. The trial protocol appears in Supplement 1.

Study Design and Treatment

This multicenter, open-label, randomized phase 3 trial was designed to test the efficacy and safety of TTFields in combination with temozolomide for treatment of glioblastoma after initial treatment with chemoradiation. After the completion of treatment with temozolomide and radiotherapy, patients were randomized at a ratio of 2 to 1 (Figure 1) to receive standard maintenance temozolomide chemotherapy (150-200 mg/m^2/d for 5 days every 28 days for 6-12 cycles according to the protocol[1] from the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group) with or without the addition of TTFields. Treatment with TTFields was to be initiated within 4 to 7 weeks from the last dose of concomitant temozolomide and radiotherapy. Randomization was performed through a central web-based randomization system and was stratified by extent of resection (biopsy, partial resection, gross total resection) and by O^6-methylguanine-DNA methyltransferase (*MGMT*) methylation status (methylated, unmethylated, or unknown).

For patients with available paraffin-embedded tumor tissue, evaluation of *MGMT* gene promoter methylation status was performed as described previously[7,15,16] by a central laboratory blinded to treatment group (MDxHealth). If *MGMT* methylation status could not be determined centrally prior to randomization, local *MGMT* methylation status was used for stratification.

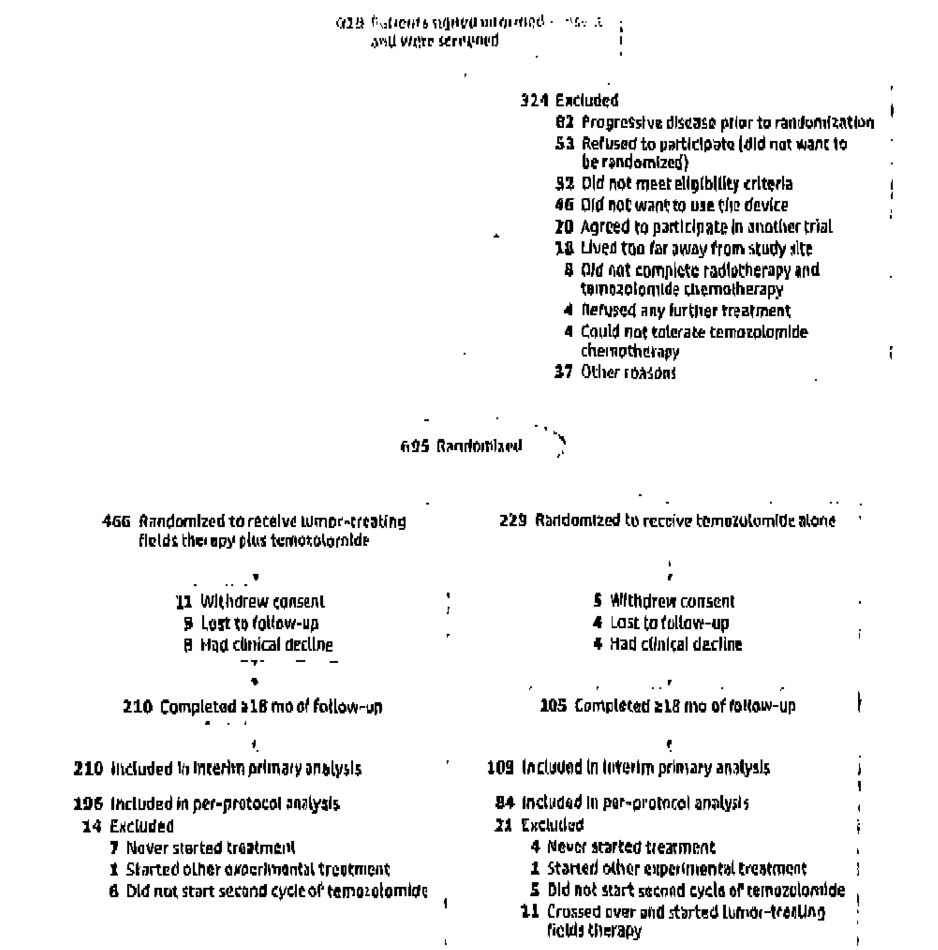
Patients in the TTFields plus temozolomide group received continuous TTFields combined with standard maintenance temozolomide. Patients receiving TTFields had 4 transducer arrays placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain (Optune, Novocure Ltd). Transducer array layouts were determined using a mapping software system for TTFields to optimize field intensity within the treated tumor (NovoTAL, Novocure Ltd). After being trained to operate the device, the patient continued treatment at home. The transducer arrays were supplied in sterile packaging and replaced by the patient, a caregiver, or a device technician twice per week. Although uninterrupted treatment was recommended, short treatment breaks for personal needs were allowed.

If a patient experienced tumor progression, second-line chemotherapy was offered per local practice. However, in the TTFields plus temozolomide group, TTFields could be continued until the second radiological progression, or clinical deterioration, for a maximum of 24 months.

Patient Surveillance and Follow-up

Baseline contrast-enhanced magnetic resonance imaging (MRI) of the brain was required within 2 weeks before starting treatment with maintenance temozolomide with or without TTFields. A complete physical examination with collection of laboratory parameters was performed within 1 week of treatment initiation. The evaluation also included a quality-of-life questionnaire (QLQ-C30) that has a brain-specific module (BN-20), which was developed by the European Organisation

Figure 1. Recruitment and Inclusion of Patients in the Study



for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups.[17,18] A Mini-Mental State Examination (a short bedside test used to evaluate cognition and memory) also was administered (a test result of 27-30 points is considered normal function).

Patients were seen monthly for medical follow-up and routine laboratory examinations. Quality of life was assessed every 3 months. Magnetic resonance imaging was to be performed every second month after the baseline MRI until second radiological progression in all patients. In the event of clinical progression, MRI was to be performed within 1 week after the study investigator became aware of it. All MRIs were reviewed centrally by 2 blinded independent radiologists (BioClinica Inc) and were evaluated for tumor response and progression using the criteria developed by Macdonald et al.[19] In cases in which the central reviewers were not in agreement, a third blinded radiologist adjudicated between them. The third radiologist was involved in 17% of the cases in the TTFields plus temozolomide group and in 18% of the cases in the temozolomide alone group.

The results of the central review were not communicated to the study investigator, and all treatment decisions were based on local imaging interpretation. Eight patients in the TTFields plus temozolomide group (4%) compared with 6 patients in the temozolomide alone group (3%) were considered stable by blinded central review; however, treatment had been changed by the study investigator due to local interpretation of tumor progression. Patients were removed from the progression-free survival analysis at the date of treatment change when this occurred before evidence of tumor progression or when patients reached the cutoff date without tumor progression.

Adverse events were recorded prospectively according to the National Cancer Institute's Common Terminology Criteria (version 3.0) until 2 months after treatment discontinuation. Adverse events are presented descriptively as number and percentage of patients with each adverse event term for all patients available at the time of the interim analysis. Treatment adherence with TTFields was recorded electronically by the device as average daily use in hours per day and information was reviewed and transferred at the monthly follow-up visit.

Statistical Considerations

The primary end point was progression-free survival in the intent-to-treat (ITT) population assessed by an independent review panel (80% power; hazard ratio [HR], 0.78; 2-sided α level

of .05). The study was also designed to have 80% power (HR, 0.76; 2-sided α level of .05) to examine overall survival as a secondary end point. To avoid an increase in the risk of a false-positive result, overall survival was to be tested statistically only if the primary end point was met.

This prespecified interim analysis was to be performed after the first 315 randomized patients reached a minimum 18-month follow-up. The final type I error rate of 0.05 was split between the interim and final analyses based on a standard α spending function.[20-22] The protocol prespecified that overall survival would be analyzed in an as-treated population, excluding all patients in both treatment groups who (1) never started maintenance temozolomide, (2) had major protocol violations, (3) crossed over to the other treatment group, or (4) received TTFields outside the protocol setting.

The primary end point would be achieved in the interim analysis if progression-free survival in the ITT population was significantly longer in the intervention group compared with the control group using a stratified log-rank test with an α level of .01. The secondary end point would be achieved in the interim analysis if overall survival in the as-treated population (per-protocol population) was significantly longer in the TTFields plus temozolomide group using a stratified log-rank test with an α level of .006. The confidence intervals that go with the HRs are presented as 1 minus the prespecified α level for each analysis. For example, the α level in the per-protocol interim analysis for overall survival was .006. Therefore, the corresponding confidence interval used for presenting the HRs was 1.000 − 0.006 (99.4% confidence interval). An upper confidence limit of less than 1 indicates the prespecified statistical threshold was met. An independent data and safety monitoring committee was chartered to stop the trial if the interim analysis of progression-free survival (ITT population) and overall survival (per-protocol population) surpassed these predetermined thresholds, as well as for futility or safety concerns.

In addition to these prespecified analyses, an analysis of overall survival in the ITT population was performed. Furthermore, a robustness analysis including all 695 patients enrolled in the trial served to validate the findings of the interim analysis (database lock: December 29, 2014; eAppendix 1 in Supplement 2).

Multiple imputation analyses also were performed for the trial's primary end point of progression-free survival in the ITT population to test the sensitivity of the results to possible bias using informative and interval censoring. These analyses included (1) treating all patients with informative censoring as treatment failures in the TTFields plus temozolomide group, (2) censoring all patients with informative censoring in the temozolomide alone group (worst case scenario), and (3) treating all events in the TTFields plus temozolomide group and in the temozolomide alone group as occurring differentially at different periods during the inter-MRI interval before the date of tumor progression.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 3.1.1.[23] The final analysis will be performed when all 695 patients enrolled in the study have at least 18 months of follow-up and will include prespecified subgroup analyses and additional secondary end points, including quality of life.

Results

Study Participants

Between July 2009 and November 2014, there were 695 patients with newly diagnosed glioblastoma randomized to receive either TTFields plus temozolomide (n = 466) or temozolomide alone (n = 229). Data for the interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 to temozolomide alone (Figure 1; database lock: September 5, 2014). The independent data and safety monitoring committee met in October 2014 to review the interim analysis; the trial met the predefined boundaries for success (improvement of both progression-free and overall survival) and the committee recommended study termination, thus allowing patients in the control group to crossover and receive TTFields.

After approval of study termination by the US Food and Drug Administration, the trial was closed to recruitment on November 29, 2014, after 695 patients of the planned 700 patients had already been randomized. All patients in the control group with ongoing maintenance therapy were offered to receive TTFields. At the time of this report, 35 patients in the control group crossed over to receive TTFields. Follow-up for all patients continues according to the protocol.

Patient baseline characteristics were well balanced between the 2 groups (Table 1). The median age was 57 years and 66% were male. The median KPS score was 90%. Sixty-four percent of patients had a gross total resection and 11% had only a diagnostic biopsy. Tumor tissue for central *MGMT* testing was available for 72% of the patients; the *MGMT* methylation frequency was 39% (75/191 valid tests; 39% for the TTFields plus temozolomide group and 41% for the temozolomide alone group). Tumor location in the brain was also comparable.

Carmustine wafers (Gliadel) were used at initial surgery in 2.4% of patients in the TTFields plus temozolomide group vs 2.9% of patients in the temozolomide alone group. Ninety-five percent of the patients were white and 61% were treated in the United States. The rest of the patients were treated at centers in Canada, Europe, Israel, and South Korea. The median time from diagnosis to randomization was 3.8 months (range, 2.0-5.7 months) for patients in the TTFields plus temozolomide group and 3.8 months (range, 1.4-5.7 months) for those in the temozolomide alone group. The median time from the end of treatment with temozolomide and radiotherapy to randomization was 36 days in the TTFields plus temozolomide group and 38 days in the temozolomide alone group; 53% of patients were randomized after having started the first cycle of maintenance temozolomide. The median time from randomization to initiation of TTFields was 5 days.

Treatment Delivery

All patients had completed radiotherapy and concomitant temozolomide as per local practice. The median number of temozolomide cycles until evidence of first tumor progression was 6 cycles (range, 1-26 cycles) for patients in the TTFields

Table 1. Patient Baseline Characteristics and Treatment Details

	All Patients (N = 315)	TTFields Plus Temozolomide (n = 210)	Temozolomide Alone (n = 105)
Age, y			
Mean (SD)	55.8 (11.1)	55.3 (11.3)	56.8 (10.5)
Median (range)	57 (20-83)	57 (20-83)	58 (21-80)
Karnofsky Performance Status score, median (range), %[a]	90 (60-100)	90 (60-100)	90 (70-100)
Sex, No. (%)			
Male	207 (66)	140 (67)	67 (64)
Female	108 (34)	70 (33)	38 (36)
Use at baseline, No. (%)			
Antiepileptic medication	126 (40)	88 (42)	38 (36)
Corticosteroid therapy	77 (24)	51 (24)	26 (25)
Mini-Mental State Examination score, No. (%)[b]			
≤26	45 (15)	31 (15)	14 (13)
27-30	247 (78)	174 (83)	73 (70)
Unknown	23 (7)	5 (2)	18 (17)
Extent of resection, No. (%)			
Biopsy	34 (11)	23 (11)	11 (10)
Partial resection	79 (25)	52 (25)	27 (26)
Gross total resection	202 (64)	135 (64)	67 (64)
Tissue available and tested, No. (%)	227 (72)	152 (72)	75 (71)
MGMT methylation	75 (33)	49 (32)	26 (35)
No methylation	116 (51)	79 (52)	38 (51)
Invalid test result	36 (16)	24 (16)	11 (15)
Region, No. (%)			
United States	191 (61)	127 (60)	64 (61)
Rest of world	124 (39)	83 (40)	41 (39)
Completed radiation therapy, No. (%)			
<57 Gy	18 (6)	13 (6)	5 (5)
60 Gy (standard; ±5%)	291 (92)	191 (91)	100 (95)
>63 Gy	6 (2)	6 (3)	0 (0)
Concomitant temozolomid use, No. (%)			
Yes	308 (98)	207 (99)	101 (96)
Unknown	7 (2)	3 (1)	4 (4)
Time from event to randomization, median (range), d			
Last day of radiotherapy	37 (13-68)	36 (13-53)	38 (13-68)
Initial diagnosis	114 (43-171)	115 (59-171)	113 (43-170)
No. of maintenance temozolomide cycles until first tumor progression, median (range)	6 (1-26)	6 (1-26)	4 (1-24)
Duration of treatment with TTFields, median (range), mo	9 (1-58)	9 (1-58)	
Adherence to TTFields therapy ≥75% during first 3 mo of treatment		157 (75)	

Abbreviations: *MGMT*, O^6-methylguanine-DNA methyltransferase; TTFields, tumor-treating fields.

[a] A higher score indicates better functional status.

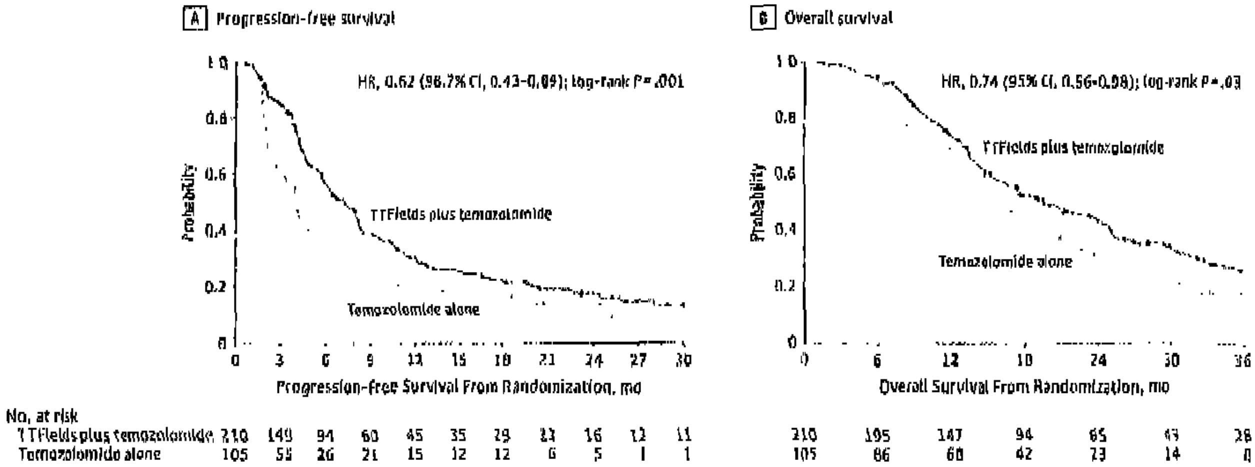
[b] A higher score indicates better cognitive capability.

plus temozolomide group and 4.0 cycles (range, 1-24 cycles) for patients in the temozolomide alone group; the median duration of treatment with TTFields was 9 months (range, 1-58 months). Two-thirds (n = 141) of patients in the TTFields plus temozolomide group continued treatment with TTFields after first tumor progression. Three-quarters (n = 157) of patients receiving treatment with TTFields were adherent to therapy (ie, wearing the device >18 hours per day on average during the first 3 treatment months).

Efficacy End Points

As prespecified, the primary end point for the efficacy results was based on progression-free survival in the ITT population of the interim analysis data set. After a median follow-up of 38 months (range, 18-60 months), the median progression-free survival from randomization was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group compared with 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (HR, 0.62 [98.7% CI, 0.43-0.89];

Figure 2. Survival Curves for Patients Included in the Interim Analysis in the Intent-to-Treat Population



Survival analyses on time from date of randomization until tumor progression, death, or last follow-up (censored patients) according to the Kaplan-Meier method. The small vertical ticks on the curves indicate censored patients. HR indicates hazard ratio; TTFields, tumor-treating fields.

stratified log-rank $P = .001$; Figure 2A). Thus, adding TTFields to temozolomide treatment increased median progression-free survival in the ITT population by 3.1 months.

As per the statistical analysis plan, overall survival was to be tested in a prespecified per-protocol population only after the primary end point was found to surpass the threshold for significance in the interim analysis. Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFields plus temozolomide group (n = 196) compared with 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group (n = 84) (HR, 0.64 [99.4% CI, 0.42-0.98]; stratified log-rank $P = .004$). The details on the per-protocol population and analyses are summarized in eAppendix 2 in Supplement 2.

In additional analyses in the ITT population, the median overall survival was 19.6 months (95% CI, 16.6-24.4 months) in the TTFields plus temozolomide group compared with 16.6 months (95% CI, 13.6-19.2 months) in the temozolomide alone group (HR, 0.74 [95% CI, 0.56-0.98]; stratified log-rank $P = .03$; Figure 2B). The percentage of patients alive at 2 years following enrollment was 43% in the TTFields plus temozolomide group and 29% in the temozolomide alone group ($P = .006$).

To assess the robustness of the interim analysis findings, additional analyses on all 695 patients randomized were performed. Patient characteristics of all patients randomized did not differ significantly from the interim data set, and the results for the main end points were similar in these analyses compared with the interim analysis (eAppendix 1 in Supplement 2).

Second-line treatments, such as nitrosoureas, temozolomide rechallenge, and bevacizumab, were received by 67% of the patients in the TTFields plus temozolomide group compared with 57% in the temozolomide alone group; about 40% of second-line therapies included bevacizumab and about 40% included nitrosoureas. The type of chemotherapy used at recurrence was balanced between treatment groups.

Secondary imputation analyses of progression-free survival with relation to the effects of interval and informational censoring did not change the conclusions of the primary progression-free survival analysis (eAppendix 3 in Supplement 2).

Safety and Tolerability

The addition of TTFields to temozolomide therapy in patients with newly diagnosed glioblastoma was not associated with any significant increase in systemic toxic effects compared with temozolomide therapy alone (Table 2). The overall incidence, distribution, and severity of adverse events were similar in patients treated with TTFields plus temozolomide and in those treated with temozolomide alone. The only notable exception was a higher incidence rate of localized skin toxicity (medical device site reaction beneath the transducer arrays) in patients treated with TTFields plus temozolomide. Mild to moderate skin irritation was observed in 43% of patients treated with TTFields plus temozolomide and severe skin reaction (grade 3) in 2%. Mild anxiety, confusion, insomnia, and headaches were reported more frequently in the patients treated with TTFields plus temozolomide and occurred mainly at the time of therapy initiation. The incidence of seizures was almost identical in the 2 groups (15 [7%] in the TTFields plus temozolomide group vs 8 [8%] in temozolomide alone group). A total of 12 patients died of causes considered unrelated to treatment while receiving adjuvant therapy (8 [3.9%] in the temozolomide plus TTFields group and 4 [4.0%] in the temozolomide alone group; Table 2).

Discussion

Glioblastoma is a highly aggressive brain tumor affecting men and women, frequently at the peak of life. Prognosis remains poor with no major treatment advance in more than a decade. In the interim analysis of this randomized clinical trial,

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the addition of TTFields to standard maintenance temozolomide significantly improved progression-free and overall survival. The prespecified analyses revealed that patients randomized to receive TTFields plus temozolomide compared with patients randomized to receive temozolomide alone had a median progression-free survival of 7.1 months vs 4.0 months (ITT analyses). Patients who received TTFields plus temozolomide had a median overall survival of 20.5 months compared with 15.6 months in those who received temozolomide alone (as per the prespecifed per-protocol analysis; the ITT analysis did not differ substantially).

Based on the results of this planned interim analysis, the trial's independent data and safety monitoring committee recommended termination of the trial. Because almost all patients had been enrolled (695/700) in the study by the time the recommendation was implemented, the full trial population will be followed up for both progression-free and overall survival. Subsequent analyses of all secondary end points and subgroups will be performed when the follow-up data are available.

The trial population and the results in the control group in this study were comparable with other glioblastoma clinical trials. Nevertheless, patients in this trial were randomized only after the end of radiochemotherapy, and for most, the first cycle of maintenance temozolomide had been started at the time of randomization; thus, patients with early tumor progression during radiochemotherapy were excluded. Most glioblastoma trials have reported survival from the date of initial diagnosis or study enrollment before starting radiochemotherapy, thus 3 to 4 months before randomization of the current study.

When the interval from diagnosis to randomization is added to the outcome results in this study, the progression-free survival of 7.8 months in the control group is comparable with most other reported studies, and supports the generalizability of these results. The Radiation Therapy Oncology Group (RTOG) 0525 protocol randomized patients only after the end of treatment with temozolomide and radiotherapy, similar to our study.[3] The control groups with standard dose temozolomide only in these 2 trials were comparable: progression-free survival from randomization of 4.0 months in the present study and 5.5 months in the RTOG 0525 trial and overall survival of 16.6 months in both trials. Thus, the benefit observed with TTFields cannot be simply attributed to patient selection. In the present trial, the gain of 3 months in both median progression-free survival (from 4.0 months to 7.2 months; HR, 0.62) and median overall survival (from 16.6 months to 19.6 months; HR, 0.74), translating into a survival gain at 2 years of 14% (from 29% to 43%) in the ITT population is in the range of benefit that is considered clinically meaningful for therapeutic agents in oncology.

The prespecified analysis for overall survival in the interim analysis was to be based on the per-protocol population (n = 280); ie, removal in both study groups of the patients who did not start their second course of maintenance temozolomide or had major protocol violations. This analysis met the prespecified threshold for efficacy in the interim analysis for the per-protocol population. In a more conservative analysis using the ITT population, an overall survival benefit was also manifest. Furthermore, an analysis of robustness performed on all randomized patients enrolled at the time

Table 2. Grade 3 to 4 Treatment-Emergent Adverse Events

	No. (%) of Patients With Adverse Events[a]	
	TTFields Plus Temozolomide (n = 203)[b]	Temozolomide Alone (n = 101)[c]
Hematological disorders[d]	25 (12)	9 (9)
Anemia	1 (<1)	2 (2)
Leukopenia or lymphopenia	11 (5)	5 (5)
Neutropenia	6 (3)	1 (1)
Thrombocytopenia	19 (9)	3 (3)
Cardiac disorders	2 (1)	3 (3)
Eye disorders	2 (1)	1 (1)
Gastrointestinal disorders[d]	11 (5)	2 (2)
Abdominal pain	2 (1)	0
Constipation	2 (1)	0
Diarrhea	1 (<1)	2 (2)
Vomiting	3 (1)	1 (1)
General disorders	17 (8)	5 (5)
Fatigue	8 (4)	4 (4)
Infections	10 (5)	5 (5)
Injury and procedural complications[d]	14 (7)	5 (5)
Fall	6 (3)	2 (2)
Medical device site reaction	4 (2)	0
Metabolism and nutrition disorders	7 (3)	3 (3)
Musculoskeletal disorders	8 (4)	3 (3)
Nervous system disorders[d]	45 (22)	25 (25)
Seizure	15 (7)	8 (8)
Headache	4 (2)	2 (2)
Psychiatric disorders[d]	9 (4)	3 (3)
Anxiety	2 (1)	0
Bradyphrenia	0	1 (1)
Confusional state	2 (1)	1 (1)
Mental status changes	4 (2)	1 (1)
Psychotic disorder	2 (1)	0
Respiratory disorders	4 (2)	1 (1)
Skin disorders	0	1 (1)
Vascular disorders[d]	8 (4)	8 (8)
Deep vein thrombosis	1 (<1)	3 (3)
Pulmonary embolism	4 (2)	6 (6)

Abbreviation: TTFields, tumor-treating fields.

[a] Safety is reported on patients who have received any treatment. Randomized patients who never received any maintenance therapy were excluded from this safety analysis.

[b] Eight patients died while receiving adjuvant therapy due to causes unrelated to therapy (1 patient for each of the following reasons: cardiac events, pulmonary emboli, respiratory, and infection; and 4 patients with central nervous system disorders likely due to tumor progression).

[c] Four patients died while receiving adjuvant therapy due to causes unrelated to therapy (1 patient for each of the following reasons: cardiac events, pulmonary emboli, respiratory, and unknown).

[d] Patients may have had more than 1 adverse event so subcategories do not total and not all events are subcategorized.

of study termination (eAppendix 1 in Supplement 2) supports the conclusions of the interim analysis.

This clinical trial has some important limitations. Patient enrollment occurred only after the end of radiochemotherapy, leading to some variation in the delivery of standard treatment of temozolomide and radiotherapy. Patients who had progressed early during radiochemotherapy were not eligible for randomization, thus excluding patients with very poor prognoses. There is likely reporting bias for second-line therapies after tumor progression because in the TTFields plus temozolomide group, TTFields were to be continued, and thus, more detailed treatment information has been tracked for this group.

This analysis reports a planned interim analysis on data from the first 315 patients with at least 18 months of follow-up; however, for detailed and meaningful subgroup analyses, the mature data of the full data set will be needed. Treatment failure patterns, effects of second-line therapies, and additional molecular analyses on baseline tumor biopsies will allow for better understanding of the clinical effects of this novel treatment modality. With the last patient randomized on November 29, 2014, however, these data are not expected before the end of 2016.

This was an open-labeled study. A sham or placebo treatment for the control group was considered neither practical (patients would be able to sense heat when they were receiving TTFields) nor appropriate (due to the burden for patients and caregivers and the need to shave the scalp and have transducer arrays placed). In this respect, the trial resembles studies evaluating radiation therapy. This raises the question of a placebo effect leading to the improved outcome. Although some effect of placebo may be expected on subjective end points, such as cognitive function and quality of life, objective end points, such as overall and progression-free survival (assessed by a blinded review panel), are independent of placebo effects in cancer therapy.[24] The panel did not have information on treatment received and no stigmata of TTFields array pads were evident on MRI.

Recent randomized studies of patients with glioblastoma, which did not use placebo controls, failed to show any increase in progression-free or overall survival[3,7] despite intensive treatment regimens requiring twice weekly hospital visits.[7] The magnitude of effect size seen in the present trial (HR of 0.62 for progression-free survival and 0.74 for overall survival) is beyond what could be attributed to a placebo effect. In addition, the support provided to patients in the TTFields plus temozolomide group by device support specialists during the trial was largely technical in nature and did not include medical supportive care. Medical follow-up with monthly visits was the same for both treatment groups.

Because TTFields were applied only to the head, an increase in systemic adverse events was neither seen nor expected. No increase in seizure rate or neurological adverse events was observed. Almost half of the patients treated with TTFields did experience some grade 1 to 2 (mild to moderate) localized skin reaction related to the application of the transducer arrays used to deliver the TTFields. This adverse effect could be managed using published skin care guidelines for patients receiving TTFields.[25] Only 2% of patients receiving TTFields had grade 3 to 4 (severe) skin reactions beneath the transducer arrays.

Conclusions

In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

ARTICLE INFORMATION

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Author Contributions: Drs Stupp and Ram had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Stupp, Kirson, Weinberg, Palti, Ram.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Stupp, Kirson, Ram.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Steinberg.

Obtained funding: Palti.

Administrative, technical, or material support: Stupp, Kirson, Weinberg, Hegi, Ram.

Study supervision: Stupp, Kirson, Weinberg, Hegi, Ram.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Stupp reported receiving travel assistance from Novocure for data review and presentation of the results at medical meetings; and receiving personal fees for serving on advisory boards for Roche/Genentech, Merck KGaA, Merck & Co, and Novartis. Dr Taillibert reported receiving personal fees from Mundipharma EDO and Roche. Dr Kanner reported receiving institutional grant funding and personal fees for speaking and device training from Novocure. Dr Kesari reported receiving institutional grant funding and personal fees for consulting and attending advisory meetings from Novocure. Dr Steinberg reported receiving consulting fees from Novocure for performing the statistical analysis. Dr Toms reported receiving personal fees from Novocure for serving on an advisory board. Dr Lieberman reported receiving institutional grant funding from Novocure. Dr Fink reported receiving personal fees from Novocure for serving on an advisory board; and receiving personal fees from Genetech for serving in the speakers program. Dr Zhu reported receiving institutional grant funding and personal fees from Novocure. Dr Engelhard reported receiving institutional grant funding and personal fees from Novocure. Dr Chen reported receiving grant funding, personal fees, nonfinancial support, and being a stock holder and chief

oncology officer in Pharmo-Kinesis; and receiving grant funding, personal fees, nonfinancial support, and being a stock holder in and CEO of NeOnc Technologies. Dr David Tran reported receiving grant funding from Celldex, NWBiotech, Novocure, and Merck; and receiving personal fees from Novocure and prIME Oncology. Dr Hottinger reported receiving travel reimbursement and speakers fees from Novocure and Merck Sharp & Dohme; and receiving personal fees for serving on an advisory board for Roche. Dr Landolfi reported receiving personal fees from Novocure for serving on an advisory board. Dr Honnorat reported receiving trial support from Novocure and serving on an advisory board for Novocure. Dr Idbaih reported receiving grants from Fondation ARC pour la recherche sur le Cancer; receiving research support from IntselChimos and Beta-Innov; receiving personal fees from Novartis for attending a conference; receiving travel reimbursement from Hoffmann-La Roche; and serving as an editorial advisory board member for Lettre du Cancérologue. Drs Kirson, Weinberg, and Palti reported being employees of Novocure. Dr Palti also reported holding 35 issued US patents and minority stock ownership in Novocure. Dr Hegi reported receiving institutional grant funding from Novocure, Merck Sharp & Dohme, Roche, and Merck-Serono; and nonfinancial support from MDxHealth for sample testing. Dr Ram reported receiving institutional grant funding from Novocure; and serving as a paid consultant for and holding stock options in Novocure. Drs Taylor, Silvani, Barnett, Henson, Sroubek, Nam Tran, Desai, Caroli, and Kew reported having no disclosures.

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Role of the Funder/Sponsor: Novocure Ltd had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The study was designed by the first and last authors (R.S. and Z.R.), together with representatives from Novocure (mainly E.D.K.). The study oversight was supported and monitored by a clinical research organization (CRO), who also holds the database. Data were collected by the investigators and monitored by the CRO. Device usedata were downloaded monthly and transferred to the study investigators or their research staff by device support specialists from Novocure Ltd. The data were analyzed separately by the statistician of the independent data monitoring committee and the study statistician (D.M.S.). Data interpretation was the responsibility of the first and last authors (R.S. and Z.R.), together with the study sponsor representative and project lead (E.D.K.). These 3 physicians also jointly developed the first draft. A subsequent mature draft and a prefinal version were circulated among all authors who gave additional input, contributed to, and approved the manuscript. The first and last authors (R.S. and Z.R.) and E.D.K. had full access to all data, and also reviewed all patient profiles for consistency (R.S. and E.D.K.). The decision to publish the data followed the independent data and safety monitoring committee recommendation for data release, and was supported by all coauthors. The roles of employees of Novocure are described in the respective author contributions. Other employees' involvement was limited to technical support of the device.

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Indications For Use and Safety Information in the United States:
Please visit www.optune.com/IFU for Optune Instructions For Use (IFU) for complete information regarding the device's indications, contraindications, warnings and precautions.

Optune is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).

Optune with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery, and completion of radiation therapy together with concomitant standard of care chemotherapy.

For the treatment of recurrent GBM, Optune is indicated following histologically-or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

Summary of Important Safety Information
Contraindications
Do not use Optune in patients with an active implanted medical device, a skull defect (such as, missing bone with no replacement), or bullet fragments. Use of Optune together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune ineffective.
Do not use Optune in patients that are known to be sensitive to conductive hydrogels. In this case, skin contact with the gel used with Optune may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings and Precautions
Optune can only be prescribed by a healthcare provider that has completed the required certification training provided by Novocure (the device manufacturer).

Do not prescribe Optune for patients that are pregnant, you think might be pregnant or are trying to get pregnant, as the safety and effectiveness of Optune in these populations have not been established.

The most common (≥10%) adverse events involving Optune in combination with temozolomide were thrombocytopenia, nausea, constipation, vomiting, fatigue, medical device site reaction, headache, convulsions, and depression.

Use of Optune in patients with an inactive implanted medical device in the brain has not been studied for safety and effectiveness, and use of Optune in these patients could lead to tissue damage or lower the chance of Optune being effective.

If the patient has an underlying serious skin condition on the scalp, evaluate whether this may prevent or temporarily interfere with Optune treatment.

Indications for use and safety information in Europe:
Newly diagnosed GBM
Optune is intended for the treatment of patients with newly diagnosed GBM, after surgery and radiotherapy with adjuvant temozolomide, concomitant to maintenance temozolomide. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after surgery and radiation therapy with adjuvant temozolomide. Treatment may be given together with maintenance temozolomide (according to the prescribing information in the Temodar package insert) and after maintenance temozolomide is stopped.

Recurrent GBM
Optune is intended for the treatment of patients with recurrent GBM who have progressed after surgery, radiotherapy and temozolomide treatment for their primary disease. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after the latest surgery, radiation therapy or chemotherapy.

Contraindications
Do not use Optune if you are pregnant, think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune was not tested in pregnant women. Do not use Optune you have clinically significant hepatic, renal or haematologic disease. Do not use Optune you have significant additional neurological disease (primary seizure disorder, dementia, progressive degenerative neurological disorder, meningitis or encephalitis, hydrocephalus associated with increased intracranial pressure). Do not use Optune if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune Treatment Kit may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings and Precautions
Use Optune only after receiving training from qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by the device manufacturer (Novocure). All servicing procedures must be performed by qualified and trained personnel.

Do not use Optune Treatment Kit if you are 17 years old or younger. The system has not been tested in persons 17 years old or younger. It is unknown what side effects the device may cause in these cases or if it will be effective.
Do not wet the device or the transducer arrays. Do not use any parts that do not come with the Optune treatment kit, or that were not sent to you by the device manufacturer or given to you by your doctor.

Optune commonly causes skin irritation beneath the transducer arrays and in rare cases lead to headaches, falls, fatigue, muscle twitching or skin ulcers.
For complete information regarding Optune's indication, contraindication, warnings and precautions please see the Instructions for Use (IFU). (http://www.optune.com/droutsch/materialien/schulungen.aspx)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

October 05, 2015

Novocure, Ltd.
℅ Mr. Jonathan S. Kahan
Partner
Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004

Re: P100034/S013
Trade/Device Name: Optune™ (Formerly the NovoTTF-100A System)
Filed: April 10, 2015
Amended: July 23, 2015
Product Code: NZK

Dear Mr. Jonathan S. Kahan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement for the Optune™ (formerly the NovoTTF-100A System). This device is indicated as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy. Optune™ was previously approved in 2011 for the treatment of recurrent GBM with the following Indications for Use (IFU): Optune™ is indicated following histologically-or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted. We are pleased to inform you that the PMA supplement is approved. You may begin commercial distribution of the device as modified in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is

therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84. This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final UDI rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. For more information on these requirements, please see the UDI website, http://www.fda.gov/udi.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at http://www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in 6 copies, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Daryl Kaufman at 301-796-6467 or Daryl.Kaufman@fda.hhs.gov.

Sincerely yours,

Carlos L. Pena -S

Carlos L. Peña, PhD, MS
Director
Division of Neurological
and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Room –WO66-G609
Silver Spring, MD 20993-0002

NovoCure, Ltd.
% Mr. Jonathan S. Kahan
Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, N.W.
Washington, D.C. 20004

APR 8 2011

Re: P100034
NovoTTF-100A System
Filed: August 16, 2010
Amended: September 10, October 19, December 13, and December 27, 2011; and February 17, and April 8, 2011
Procode: NZK

Dear Mr. Kahan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the NovoTTF-100A System. This device is indicated for treatment of adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme, following histologically- or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Page 2 - Mr. Jonathan S. Kahan

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the conditions outline above, you must conduct the following post-approval study (PAS):

The New Enrollment Study for NovoTTF-100A in Recurrent GBM Patients: Per agreed on study outline (e-mail dated April 5, 2011) this study will address the following question: Is the overall survival of patients treated with NovoTTF-100A non-inferior to the survival of patients treated with the best standard of care (chemotherapy)? This question will be addressed with a prospective, multi-center, non-randomized, unblinded, concurrent control study of NovoTTF-100A in recurrent Glioblastoma Multiforme (GBM) patients. The study will be conducted in at least 30 sites, at least half of them in the United States, and may include centers with previous experience with the device. Patients 22 years old and older will be included in the PAS. A total of 486 subjects will be enrolled, with 243 subjects per study arm. All study participants will be followed until death. Study follow-up visits include baseline and monthly in-office visits until disease progression. Assessment at baseline includes the Mini Mental State Examination (MMSE) and genetic profiling. The monthly assessments include survival status, MMSE and adverse events assessment. After disease progression study participants will be followed by monthly phone calls to determine survival status.

The primary data analysis will compare overall survival in NovoTTF-100A patients to that seen in concurrent BSC comparison patients, in the investigational device exemption (IDE) study Intent-to-Treat population, within a predefined confidence interval bound consistent with a performance goal of 1.375. The secondary endpoints will be: Change in neuro-cognitive function from baseline based on the MMSE; Genetic profiling of tumors and correlation with response to NovoTTF-100A treatment, specifically:

- MGMT promoter methylation status
- EGFR amplification, over expression or rearrangement
- Chromosomes 1p/19q deletion status
- Adverse event incidence by body system and term, including:
- Incidence of seizures
- Anticonvulsant use

Page 3 - Mr. Jonathan S. Kahan

Please be advised that the results from these studies should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement.

In addition to the Annual Report requirements, FDA would like to remind you that you are required to submit PAS Progress Reports every six months during the first two years and annually thereafter. The reports should clearly be identified as Post-Approval Study Report. Two copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA.

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a complete protocol of your post-approval study. Your PMA supplement should be clearly labeled as a "Post-Approval Study Protocol" and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm#2

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

Page 4 - Mr. Jonathan S. Kahan

device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

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Page 5 - Mr. Jonathan S. Kahan

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing. One of those three copies may be an electronic copy (eCopy), in an electronic format that FDA can process, review and archive (general information: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.htm; clinical and statistical data: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm136377.htm)

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Mail Center -- WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Ms. Jan C. Callaway at 301-796-5620.

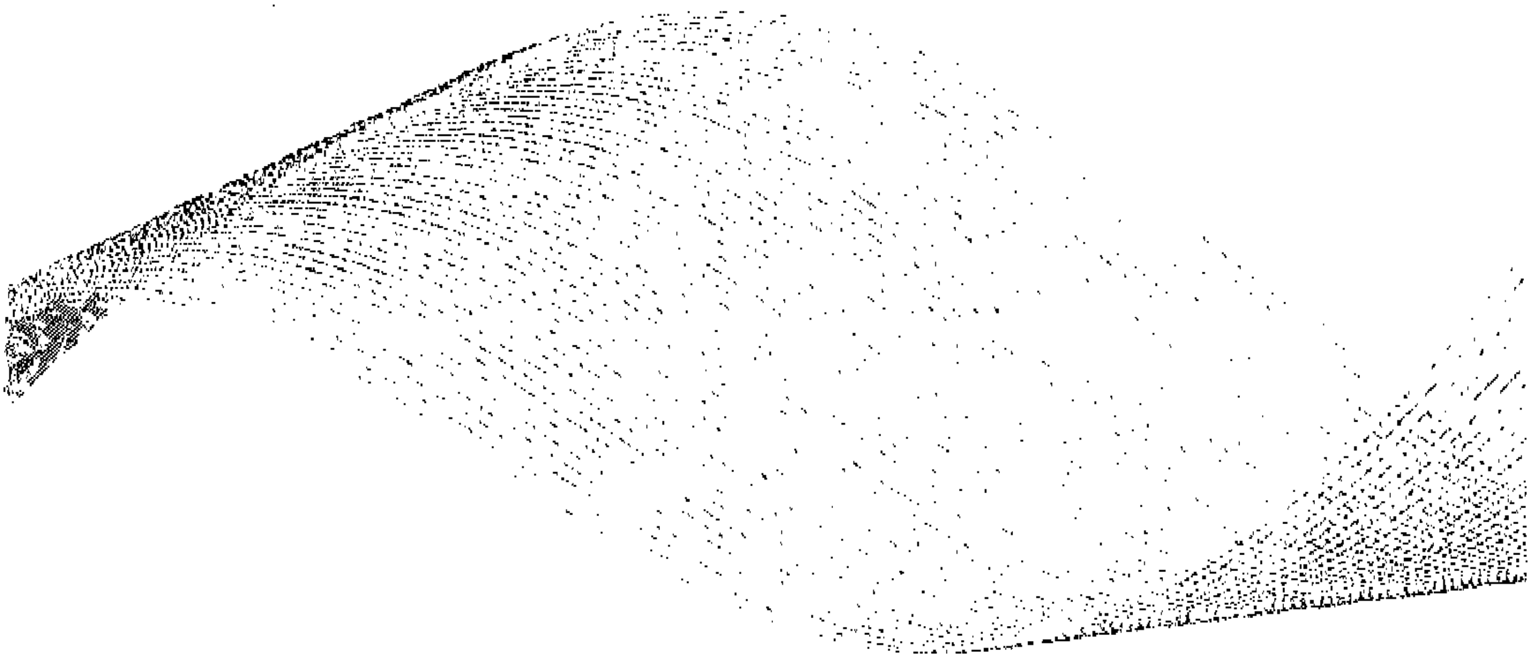
Sincerely yours,

for

Christy Foreman
Acting Director
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

OPTUNE | INSTRUCTIONS FOR USE

(NovoTTF™-100A System)



novocure™

This manual is intended for physicians prescribing the use of Optune.
Additional information is found in the following materials:

- Patient Information and Operation Manual

Caution: Federal law restricts this device to sale by or on the order of a physician.

Table of contents

Indications for Use

Optune™ Is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).

Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

For the treatment of recurrent GBM, Optune™ is indicated following histologically-or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

Contraindications, Warnings and Precautions

Contraindications

Do not use Optune if you have an active implanted medical device, a skull defect (such as, missing bone with no replacement) or bullet fragments. Examples of active electronic devices include deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers, defibrillators, and programmable shunts. Use of Optune together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune ineffective.

Do not use Optune if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings

Warning - Use Optune only after receiving training from qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by the device manufacturer (Novocure). Ask to see a certificate signed by Novocure that says they completed a training course. Your training will include a detailed review of this manual and practice in the use of the system. In addition, you will be trained in what to do if there are problems with treatment. Use of Optune without receiving this training can result in breaks in treatment and may rarely cause increased scalp rash, open sores on your head, allergic reactions or even an electric shock.

Warning - Optune is not intended to be used as a substitute for chemotherapy but rather as an adjunct to treatment with TMZ for newly diagnosed GBM.

Warning - Do not use Optune if you are 21 years old or younger. It is unknown what side effects the device may cause in these cases or if it will be effective.

Warning - Do not use Optune if you are pregnant, you think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune was not tested in pregnant women. It is unknown what side effects the device may cause if you are pregnant or if it will be effective.

Warning - In case of skin irritation, which appears as redness under the transducer arrays (a mild rash), use high potency topical steroids (hydrocortisone cream) when replacing transducer arrays. This will help relieve your skin irritation. If you do not use this cream, the skin irritation can become more serious and may even lead to skin break down, infections, pain and blisters. If this happens, stop using the topical steroid cream and contact your doctor. Your doctor will supply you with an antibiotic cream to use when replacing transducer arrays. If you do not use this cream, your symptoms may continue and your doctor may ask you to take a break from treatment until your skin heals. Taking a break from treatment may lower your chance to respond to treatment.

Warning - All servicing procedures must be performed by qualified and trained personnel. If you attempt to open and service the system alone you may cause damage to the system. You could also get an electric shock by touching the inner parts of the device.

Precautions

Caution - Keep Optune out of the reach of children. If children touch the device, they could damage the device. This could cause a break in treatment. Breaks in treatment may lower your chance to respond to treatment.

Caution - Do not use any parts that do not come with the Optune Treatment Kit, or that were not sent to you by the device manufacturer or given to you by your doctor. Use of other parts, manufactured by other companies or for use with other devices, can damage the device. This may lead to a break in treatment. Breaks in treatment may lower your chance to respond to treatment.

Caution - If your doctor used plates or screws to close your skull bone during your surgery, be careful when placing the transducer arrays. Make sure the round disks that make up the transducer arrays are not on top of the areas where you can feel the screws or plates under your skin. In other words, make sure the screws or plates under your skin are in between the round disks that make up the transducer arrays. If you do not do this, you may have increased skin damage which may lead to a break in treatment. Breaks in treatment may lower the chance of the device being effective.

Caution – Tell your doctor before using the device if you have an inactive implanted medical device in the brain (for example, stents, plastic drug delivery reservoirs, aneurysm clips or coils, device leads). Use of Optune in subjects with inactive implanted medical devices in their brain was not been tested and could lead to tissue damage or lower the chance of the device being effective.

Caution - Do not use Optune if any parts look damaged (torn wires, loose connectors, loose sockets, cracks or breaks in the plastic case). Use of damaged components can damage the device, and cause a break in treatment. Breaks from treatment may lower your chance to respond to treatment.

Caution - Do not wet the device or transducer arrays. Getting the device wet may damage it, preventing you from receiving treatment for the right amount of time. Getting the transducer arrays very wet is likely to cause the transducer arrays to come loose from your head. If this happens, the device will turn off and you will need to change the transducer arrays.

Caution - Before connecting or disconnecting the transducer arrays, make sure that the Optune power switch is in the OFF position Disconnecting transducer arrays with the device power switch in the ON position may cause a device alarm to go off, and could damage the device

Caution - If you have an underlying serious skin condition on the scalp, discuss with your doctor whether this may prevent or temporarily interfere with Optune treatment

Notices

Notice! The Optune device and transducer arrays will activate metal detectors

Notice! Do not use Optune if your tumor is located in the lower parts of the brain close to the spinal cord. Ask your doctor if your tumor is located in this part of your brain. Optune has not been tested in patients with tumors in these locations It is unknown whether these tumors will respond to treatment

Notice! You should use Optune for at least 18 hours a day to get the best response to treatment. Using Optune for less than 18 hours a day lowers the chances that you will respond to treatment.

Notice! Do not stop using Optune before you finish at least four full weeks of therapy to get the best response to treatment Stopping treatment before four weeks lowers the chances that you will respond to treatment.

Notice! Do not stop using Optune even if you have used it less than the recommended 18 hours per day. You should stop using the device only if your doctor tells you to. Stopping treatment could lower the chances that you will respond to treatment.

Notice! If you plan to be away from home for more than 2 hours, carry an extra battery and/or the power supply with you in case the battery you are using runs out If you do not take a spare battery and/or the power supply you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Make sure you have at least 12 extra transducer arrays at all times. This will last you until the next transducer array shipment arrives. Remember to order more transducer arrays when there are at least 12 extra transducer arrays left If you do not order transducer arrays in time you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Batteries may weaken over time and need to be replaced You will know this has happened when the amount of time the device can run on a fully charged battery begins to shorten. For example, if the low battery indicator light flashes within only 1.5 hours from the start of treatment, replace the battery If you do not have replacement batteries when your batteries run out, you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment

Notice! You should carry the Troubleshooting Guide (Section 26) at all times. This guide is necessary to ensure Optune works properly If you do not work the system correctly you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment

Notice! Do not block the device vents located on the sides of the Optune device Blocking the vents may cause the device to overheat and turn off, leading to a break in treatment. If this happens, unblock the vents, wait 5 minutes and restart the device

Notice! Do not block the battery charger vents located on the front of the battery chargers Blocking the vents may cause the charger to overheat. This could prevent your batteries from charging.

Notice! Before using a transducer array, make sure its package is sealed by gently rubbing the package between thumb and pointer finger on all four sides The package should be closed on all sides There should be no openings in the package seal. If the package is not sealed, the transducer array may be damaged. A damaged transducer array will not work properly and may cause the device to turn off

Notice! The transducer arrays are for single use and should not be taken off your head and put back on again If you put a used transducer array back on your head again, it may not stick well to your skin and the device could turn off

Description

Optune, for the treatment of newly diagnosed and/or recurrent GBM, is a portable battery or power supply operated device which produces alternating electrical fields, called tumor treatment fields ("TTFields") within the human body. TTFields are applied to the patient by electrically-insulated surface transducer arrays. TTFields disrupt the rapid cell division exhibited by cancer cells[1].

Optune is comprised of two main components: (1) an Electric Field Generator (the Optune device); and (2) INE Insulated Transducer Arrays (the transducer arrays). In addition, the following components are also included in the Optune Treatment Kit: power supply, portable battery, battery rack, battery charger, connection cable and carrying case.

Treatment parameters are preset by Novocure such that there are no electrical output adjustments available to the patient. The patient must learn to change and recharge depleted device batteries and to connect to an external power supply overnight. In addition, the transducer arrays need to be replaced once to twice a week and the scalp re-shaved in order to maintain optimal contact. Patients carry the device in an over-the-shoulder bag or backpack and receive continuous treatment without changing their daily routine.

1 Kirson, E. D., V. Dbaly, et al. (2007). "Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors." Proc Natl Acad Sci U S A 104(24): 10152-7

Principles of Operation

Optune produces alternating electrical fields within the human body that disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through transducer arrays placed on the scalp

TTFields harness electric fields to arrest the proliferation of tumor cells and to destroy them. The TTField technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to the effects of the alternating electric TTFields. Those special fields alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for a particular treatment is specific to the cell type being treated (e.g., 200kHz for GBM)

In contrast, the TTFields have not been shown to have an effect on cells that are not undergoing division. Since most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be little affected by the TTFields. Testing demonstrates no differences between treated and control animals in histology of the major internal organs (including the brain), blood examination, cardiac rhythm, body temperature, or in animal behavior. In addition, because the fields alternate so rapidly, they have no effect on normal quiescent cells nor do they stimulate nerves and muscles It is noted that, because TTFields are only applied to the brain, they have no effect on rapidly proliferating cells in the rest of the body. The intensities of the electric fields within the tissues are very small and do not result in any meaningful increase in tissue temperature. Thus, TTField application has the advantage of being highly selective and is not expected to be associated with significant toxicity

The above mechanisms of action are consistent with the extensive research regarding the effects of TTFields. These results demonstrate both disruption of cell division up to complete cessation of the process, as well as complete destruction of the dividing cells. It is important to note that all the described effects can be obtained by fields of low intensity such that they are not accompanied by any significant elevation of temperature.

Preclinical Data

TTFields have been shown both in vitro and in vivo to effectively inhibit cancer cell replication during mitosis without any systemic side effects. At intensities of approximately 1 V/cm, TTFields can be frequency-tuned to effectively inhibit different cancer cell types (i.e., the smaller the cell, the higher the frequency needed). Due to disruption of microtubule polymerization and physical disruption of cell integrity at the cleavage plane during telophase[2]

Specifically, TTFields have been shown to inhibit glioblastoma cells in vitro and in vivo at a frequency of 200 kHz and an intensity of 0.7 V/cm. Based on realistic finite element mesh simulations and direct measurements of TTFields intensity in experimental animals, and in the human brain, Novocure has concluded that effective TTField intensities can be generated in the brains of large animals and humans. Extensive safety studies in healthy animals (mice, rats and rabbits) have shown that TTFields are not associated with significant systemic toxicities. Neither acute, nor chronic systemic toxicities were seen when TTFields were applied to the torso or head, at different frequencies (100-200 kHz), different intensities and for different periods of time[5]

Using a model developed to simulate the growth kinetics of a malignant tumor, the minimal treatment course duration for Optune has been determined to be approximately 4 weeks to reach tumor stabilization. Stopping treatment prior to completion of a 4 week treatment course will most likely lead to continued tumor growth and appearance of symptoms within approximately 1-2 weeks.

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2 Kirson, E.D., Z. Gurvich, et al. (2004). "Disruption of cancer cell replication by alternating electric fields." Cancer Res 64(9): 3288-95. 1103

5 Kirson, E.D., V. Dbaly, et al. (2007).

Clinical Data

NEWLY DIAGNOSED GLIOBLASTOMA (see page 17 for recurrent GBM)

Pilot Clinical Study in Newly Diagnosed GBM

Optune together with temozolomide (TMZ) has been tested in ten newly diagnosed GBM subjects in a single center, pilot study in Europe. Median progression free survival (PFS) of the patients in this study exceeded historical controls (14.4 months versus 7.1 months, respectively). At the end of the study (4 years from initiation) 5 of the 10 patients died; of the remaining 5 patients 2 were lost to follow up and 3 were reported alive and progression free. Median OS from diagnosis was greater than 40 months (compared to 14.7 months in historical controls). The only device related adverse event (AE) seen in this trial was a mild to moderate skin irritation beneath the device transducer arrays.

Pivotal Clinical Study in Newly Diagnosed GBM

Study Design: The study was a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of newly diagnosed GBM subjects treated with Optune and Temozolomide (TMZ) to those treated with TMZ alone.

The following were the objectives of the study:

To prospectively compare the progression free survival and overall survival of newly diagnosed GBM subjects treated with Optune and TMZ to those treated TMZ alone.

To collect evidence of the safety of TTFields applied to subjects with newly diagnosed GBM using Optune.

Eligibility Criteria: The inclusion and exclusion criteria for the trial were as follows:

Inclusion Criteria

a. Pathological evidence of GBM using WHO classification criteria
b. ≥ 18 years of age.
c. Received maximal debulking surgery and radiotherapy concomitant with Temozolomide (45-70Gy):
   1) Patients may enroll in the study if received Gliadel wafers before entering the trial
   2) Any additional treatments received prior to enrollment will be considered an exclusion
   3) Minimal dose for concomitant radiotherapy is 45 Gy
d. Karnofsky scale ≥ 70
e. Life expectancy at least 3 months
f. Participants of childbearing age must use effective contraception
g. All patients must sign written informed consent
h. Treatment start date at least 4 weeks out from surgery.
i. Treatment start date at least 4 weeks out but not more than 7 weeks from the later of last dose of concomitant Temozolomide or radiotherapy

Exclusion Criteria

a. Progressive disease (according to MacDonald Criteria). If pseudoprogression is suspected, additional imaging studies must be performed to rule out true progression.
b. Actively participating in another clinical treatment trial
c. Pregnant
d. Significant co-morbidities at baseline which would prevent maintenance Temozolomide treatment:
   1) Thrombocytopenia (platelet count < 100 x 103/μL)
   2) Neutropenia (absolute neutrophil count < 1.5 x 103/μL)
   3) CTC grade 4 non-hematological Toxicity (except for alopecia, nausea, vomiting)
   4) Significant liver function impairment - AST or ALT > 3 times the upper limit of normal
   5) Total bilirubin > upper limit of normal
   6) Significant renal impairment (serum creatinine > 1.7 mg/dL)
e. Implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted electronic devices in the brain, or documented clinically significant arrhythmias.
f. Infra-tentorial tumor
g. Evidence of increased intracranial pressure (midline shift > 5mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)
h. History of hypersensitivity reaction to Temozolomide or a history of hypersensitivity to DTIC.

Study Procedures:

Treatment Arm

Optune was given together with maintenance TMZ. At treatment initiation patients were seen at an outpatient clinic. During this visit baseline examinations were performed and Optune treatment initiated. The patients were instructed on the operation of Optune and battery replacement. Once the patients were trained in operating the device they were released to continue treatment at home. The patients received multiple 1 month courses of continuous Optune treatment. Patients were treated with maintenance TMZ according to the standard dosing regimen. Following radiological progression or unacceptable toxicity, TMZ could be replaced with best standard of care second line therapy.

Control Arm

All subjects had baseline examinations performed prior to treatment initiation. Patients were treated with maintenance TMZ according to the standard dosing regimen. Following radiological progression or unacceptable toxicity, TMZ could be replaced with best standard of care second line therapy.

Follow-up

During treatment all patients were seen once every month at an outpatient clinic where they underwent medical follow-up and routine laboratory exams. An MRI was performed every second month following the baseline MRI until second progression or 24 months (whichever came first, when treatment on both arms of the study was terminated). In the case of clinical progression an unscheduled MRI was obtained within 1 week of the investigator becoming aware of the clinical progression. No additional MRIs were required after second progression. Central MRI review was performed by a neuro-radiologist blinded to the treatment group of each patient. Medical follow-up continued for 2 months after treatment termination in order to capture treatment related toxicities. After these visits, mortality was assessed based on monthly telephone interviews with the patients or the patients' caregivers.

Analyses: Two analyses were performed in the study: An interim analysis on the first 315 patients with a minimum of 18 months follow up and a final analysis on the full study cohort of 695 patients.

Protocol Deviations: Major protocol deviations were defined as deviations that have the potential to influence the primary and secondary efficacy endpoints of the study. There were a total of 13 major protocol deviations in the interim analysis and a total of 24 major protocol violations at the final analysis.

In the interim analysis dataset, 2 patients received experimental chemotherapies as part of other clinical trials together with their standard of care temozolomide (1 in each treatment arm). In addition, 11 patients in the TMZ alone arm received Optune treatment through prescription at other institutions. This deviation was termed "crossover" although no official crossover was allowed in the protocol, and Optune therapy was given without sponsor or investigator consent.

In the final analysis dataset, 2 patients received experimental chemotherapies as part of other clinical trials together with their standard of care temozolomide (1 in each treatment arm). In addition, 22 patients in the TMZ alone arm received Optune treatment through prescription at other institutions. This deviation was termed "crossover" although no official crossover was allowed in the protocol, and Optune therapy was given without sponsor or investigator consent.

Analysis Populations: Progression free survival was analyzed in the intent to treat (ITT) population which included all randomized subjects (210 Optune / TMZ and 105 TMZ alone at the interim analysis, 466 Optune / TMZ and 229 TMZ alone at the final analysis). Overall survival was analyzed in the per protocol (PP) population which included all patients receiving at least the first course of TMZ and had no major protocol deviations (196 Optune / TMZ and 84 TMZ alone at the interim analysis; 429 Optune / TMZ and 180 TMZ alone at the final analysis). Major protocol deviations included patients who received other experimental therapies on protocol or crossed over from the TMZ alone arm to Optune / TMZ.

Subject Characteristics: 315 subjects (210 Optune/TMZ: 105 TMZ) with newly diagnosed GBM were enrolled in the interim analysis of the study. Baseline characteristics in the ITT population were as follows:

Baseline Characteristic		Treatment Group	
		Optune/TMZ (N=210) n(%)	TMZ Alone (N=105) n(%)
Gender			
Male		140 (66.67)	67 (63.81)
Female		70 (33.33)	38 (36.19)
Central MGMT Assessment			
Invalid		24 (11.43)	11 (10.48)
Unknown		58 (27.62)	30 (28.57)
Methylated		49 (23.33)	26 (24.76)
Unmethylated		79 (37.62)	38 (36.19)
Extent of Resection			
Biopsy		23 (10.95)	11 (10.48)
Gross Total Resection		135 (64.29)	67 (63.81)
Partial Resection		52 (24.76)	27 (25.71)
Area			
ROW		83 (39.52)	41 (39.05)
USA		127 (60.48)	64 (60.95)
Tumor Position			
Missing		0 (0)	3 (2.86)
Corpus Callosum		12 (5.71)	3 (2.86)
Frontal Lobe		64 (30.48)	32 (30.48)
Occipital Lobe		7 (3.33)	4 (3.81)
Pariental Lobe		35 (16.67)	27 (25.71)
Temporal Lobe		92 (43.81)	36 (34.29)
Tumor Location			
Missing		0 (0)	1 (0.95)
Both		2 (0.95)	1 (0.95)
Corpus Callosum		8 (3.81)	3 (2.86)
Left		93 (44.29)	41 (39.05)
Right		107 (50.95)	59 (56.19)
Karnofsky Performance Score	Median	90	90
	Min, Max	60, 100	70, 100
Age in Years	Median	57	58
	Min, Max	20, 83	21, 80
No. of Cycles of TMZ Received	Median	6	4
	Min, Max	1, 26	1, 24
No. of Cycles of Optune Received	Median	9	0
	Min, Max	1, 58	0, 0
Time from GBM Diagnosis to Randomization (Days)	Median	115	113
	Min, Max	59, 171	43, 170

As seen above, all baseline characteristics are well balanced between arms in the ITT population at the interim analysis. The baseline characteristics of the PP population also remained well balanced between treatment arms. As noted in the table above, 35 patients (11.11%) had tissue that was not evaluable, and 88 patients (27.94%) did not have tissue available for analysis.

695 subjects (466 Optune / TMZ; 229 TMZ alone) with newly diagnosed GBM were enrolled in the study and had CRF information available at the time of the final analysis. Baseline characteristics in the ITT population were as follows

Baseline Characteristic		Treatment Group	
		Optune/TMZ	TMZ Alone
		(N=446)	(N=229)
		n(%)	n(%)
Gender			
Male		316 (67.81)	157 (68.56)
Female		150 (32.19)	72 (31.44)
Central MGMT Assessment			
Invalid		46 (9.87)	18 (7.86)
Unknown		106 (22.75)	57 (24.89)
Methylated		127 (27.25)	67 (29.26)
Unmethylated		187 (40.13)	87 (37.99)
Extent of Resection			
Biopsy		61 (13.09)	30 (13.1)
Gross Total Resection		253 (54.29)	124 (54.15)
Partial Resection		152 (32.62)	75 (32.75)
Area			
ROW		245 (52.58)	111 (48.47)
USA		221 (47.42)	118 (51.53)
Tumor Position			
Missing		31 (6.65)	15 (6.55)
Corpus Callosum		21 (4.51)	9 (3.93)
Frontal Lobe		142 (30.47)	67 (29.26)
Occipital Lobe		14 (3)	4 (1.75)
Pariental Lobe		77 (16.52)	50 (21.83)
Temporal Lobe		181 (38.84)	84 (36.68)
Tumor Location			
Missing		30 (6.44)	12 (5.24)
Both		12 (2.58)	3 (1.31)
Corpus Callosum		12 (2.58)	7 (3.06)
Left		193 (41.42)	93 (40.61)
Right		219 (47)	114 (49.78)
Karnofsky Performance Score	Median	90	90
	Min, Max	60, 100	70, 100
Age in Years	Median	56	57
	Min, Max	19, 83	19, 80
No. of Cycles of TMZ Received	Median		4
	Min, Max	1, 26	1, 24
No. of Cycles of Optune Received	Median	6	0
	Min, Max	1, 58	0, 0
Time from GBM Diagnosis to Randomization (Days)	Median	113	111
	Min, Max	59, 498	43, 500

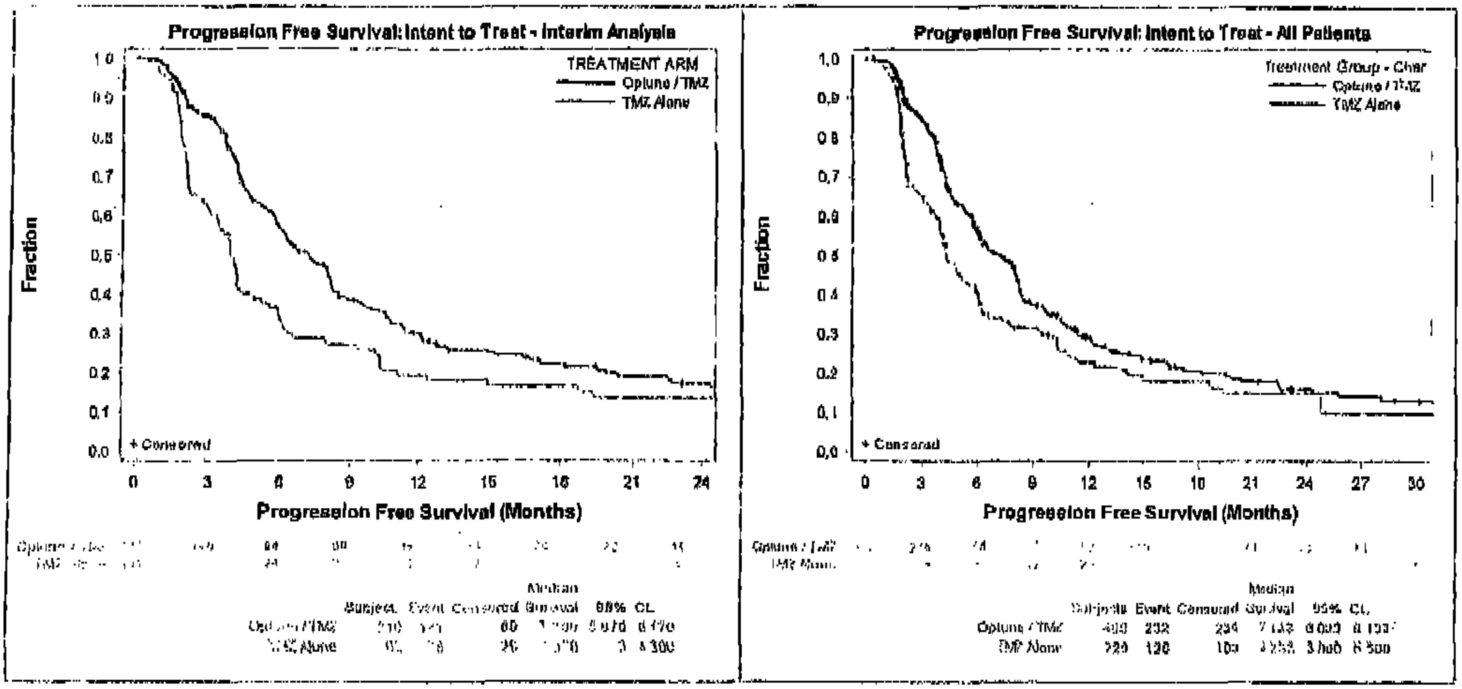
As seen above, all baseline characteristics are well balanced between arms in the ITT population at the final analysis. The baseline characteristics of the PP population also remained well balanced between treatment arms. As noted in the table above, 64 patients (9.21%) had tissue that was not evaluable, and 163 patients (23.45%) did not have tissue available for analysis.

Effectiveness Results:

Primary Effectiveness Endpoint: Progression Free Survival at the Interim Analysis

The threshold for statistical significance based on the Lan-DeMets O'Brien-Fleming method at the interim analysis was pre defined as p=0.01394, and the test was to be performed in the ITT population according to the protocol. In the ITT population, which included all randomized subjects (Optune/TMZ=210, TMZ alone=105), PFS at the interim analysis met this threshold. The difference of more than 3 months in median PFS is highly clinically significant. The Hazard Ratio for PFS was 0.621, which translates into a 37.9% decrease in the risk of progression when using Optune/TMZ compared to TMZ alone. At the final analysis, which included 695 patients (Optune/TMZ=466, TMZ alone=229), PFS was also highly significant with a hazard ratio of 0.694.

Primary Efficacy Endpoint - Progression Free Survival (ITT)



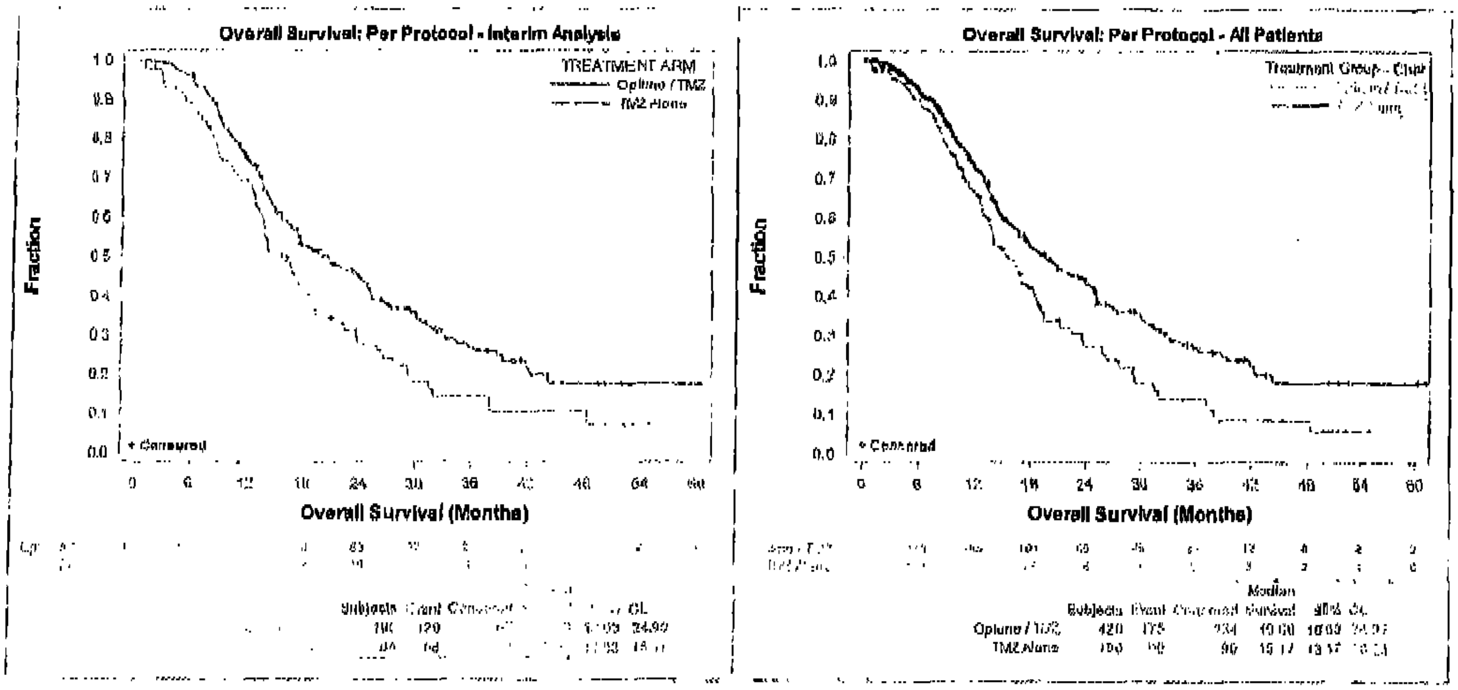
	Interim Analysis		Final Analysis	
	Optune/TMZ	TMZ Alone	Optune/TMZ	TMZ Alone
Median (95% CI)	7.2 (5.9, 8.2)	4.0 (3.0, 4.3)	7.1 (6.0, 8.1)	4.2 (3.9, 5.5)
Log-rank test	p=0.0015		p=0.0010	
Hazard Ratio (95% CI)	0.621 (0.468, 0.823)		0.694 (0.558, 0.823)	

Although not a pre-specified endpoint, PFS was also analyzed in the PP population at the interim and final analyses. Median PFS in the PP population was identical to the ITT population at the interim analysis and slightly longer than the ITT population at the final analysis. Notably, median PFS remained significantly higher in the Optune/TMZ group than in the TMZ alone group in the PP population at both the interim and final analyses.

Powered Secondary Effectiveness Endpoint: Overall Survival at the Interim Analysis

Overall survival (OS) was [illegible] secondary analysis in the trial. The threshold for superior OS at the interim analysis was predefined in the [illegible] using [illegible] DeMets / O'Brien-Fleming alpha spending function, and was to be tested in the PP population. In the PP population, which [illegible] patients according to the treatment they actually received (as treated, Optune/TMZ - 196, TMZ - 84), OS was also significantly longer in the Optune/TMZ arm compared to the TMZ alone arm. An increase of almost [illegible] months as seen here is highly significant clinically [illegible]. This translates into a [illegible] decrease in the risk of death when using Optune/TMZ compared to TMZ alone. At the final analysis, which included 609 patients (Optune/TMZ - 429, TMZ alone - 180), OS was also highly significant with a hazard ratio of 0.683.

Overall Survival (PP)



	Interim Analysis		Final Analysis	
	Optune/TMZ	TMZ Alone	Optune/TMZ	TMZ Alone
Median (95% CI)	20.5 (16.6, 24.9)	15.6 (12.9, 18.5)	19.6 (16.6, 24.1)	15.2 (13.5, 18.2)
Log-rank test	p=0.0042		p=0.0030	
Hazard Ratio (95% CI)	0.666 (0.495, 0.898)		0.683 (0.529, 0.882)	

Although not a pre-specified secondary endpoint, OS was also analyzed in the ITT population. At the interim analysis, OS in the ITT population was also significantly longer in the Optune/TMZ arm compared to TMZ alone by almost 20%. The median OS was 19.6 months (95% CI 16.5-24.1) in the Optune/TMZ group and 16.6 months in the TMZ alone group (95% CI 13.5-19.1). An increase of 3 months as seen here is highly significant both statistically (log-rank p=0.0338) and clinically. The hazard ratio for OS was 0.744 using a Cox regression analysis. This translates into a [illegible] decrease in the risk of death when using Optune/TMZ compared to TMZ alone.

Furthermore, at the final analysis, OS in the ITT population was also significantly longer in the Optune/TMZ arm compared to TMZ alone by [illegible]%. The median OS was 19.4 months (95% CI 16.5-23.8) in the Optune/TMZ group and 16.6 months in the TMZ alone group (95% CI 13.7-19.5). An increase of almost 3 months, as seen here is highly significant statistically and clinically (log-rank p=0.0229). The hazard ratio for OS was 0.754 using a Cox regression analysis. This translates into a 24.6% decrease in the risk of death when using Optune/TMZ compared to TMZ alone.

Secondary Endpoints: Secondary endpoints also showed an advantage for Optune/TMZ compared to TMZ alone. The results below are from the interim analysis which included 315 patients (210 Optune/TMZ and 105 TMZ alone):

Endpoint	Optune/TMZ	TMZ Alone	P-Value
Progression Free Survival at 6 months (ITT)	56.7%	33.7%	0.0004
1-year survival (PP)	75%	69%	0.151
2-year survival (PP)	48%	32%	0.0056
Complete response rate (ITT)	9%	3.5%	NA

In addition, although not a pre-specified endpoint, 1- and 2-year survival were also analyzed in the ITT population at the interim analysis. In the ITT population, 1-year survival was 75% in the Optune/TMZ group and 70% in the TMZ alone group (p-value=0.162) at the interim analysis. 2-year survival in the ITT population at the interim analysis was 48% in the Optune/TMZ group and 34% in the TMZ alone group (p-value=0.0122). Furthermore, the 1-year survival rates at the final analysis are shown in the table below:

Endpoint	Optune/TMZ	TMZ Alone	P-Value
1-year survival (PP)	69%	63%	0.131
1-year survival (ITT)	69%	66%	0.265

Quality of Life: Quality of Life assessments were based on the interim analysis cohort of 315 subjects. Quality of life, cognitive function and functional status were all maintained throughout treatment with the device, leading to the clear conclusion that use of Optune does not harm patients' quality of life, cognitive function or ability to perform activities of daily living.

Safety Results: Safety was assessed on all patients at the final analysis who received any treatment at the time of the analysis (Optune/TMZ: 437, TMZ alone: 207). A slightly higher incidence of grade 3-4 adverse events was seen in some of the systems in the Optune/TMZ arm of the study. This is most likely a reflection of the longer duration of TMZ treatment in these patients (median of 6 cycles versus 4 cycles in the control arm) due to the increase in PFS seen in the treatment group. Grade 3-4 adverse events were well balanced in both arms. None of the grade 3-5 adverse events in these body systems were considered related to Optune by any of the investigators, except for 1% grade 3 skin irritation.

All Adverse Events by Body System and Severity (Safety Population)

	Optune/TMZ (N=437)			TMZ Alone (N=207)		
System Organ Class	Low-Medium	Severe	Fatal	Low-Medium	Severe	Fatal
Number of Patients with ≥1 AE	211 (49%)	169 (39%)	[illegible]	[illegible]	82 (40%)	7 (3%)
Blood and Lymphatic System Disorders	86 (20%)	47 (11%)	0	49 (24%)	21 (10%)	0
Cardiac Disorders	12 (3%)	3 (1%)	3 (1%)	6 (3%)	4 (2%)	0
Ear and Labyrinth Disorders	25 (6%)	[illegible]	0	9 (4%)	0	[illegible]
Endocrine Disorders	11 (3%)	0	0	4 (2%)	0	0
Eye Disorders	36 (9%)	3 (1%)	[illegible]	15 (7%)	2 (1%)	0
Gastrointestinal Disorders	202 (46%)	18 (4%)	0	76 (37%)	4 (2%)	0
General Disorders and Administration Site Conditions	175 (40%)	27 (6%)	1 (<1%)	76 (37%)	10 (5%)	1 (<1%)
Hepatobiliary Disorders	1 (<1%)	1 (<1%)	0	5 (2%)	0	0
Liver Disorder	1 (<1%)	0	0	3 (1%)	0	0
Immune System Disorders	10 (2%)	0	0	7 (3%)	0	0
Infections and Infestations	117 (27%)	19 (4%)	3 (1%)	50 (24%)	6 (3%)	1 (<1%)
Injury, Poisoning and Procedural Complications	216 (49%)	20 (5%)	0	13 (6%)	4 (2%)	0
Abnormal Laboratory Tests	58 (13%)	19 (4%)	0	26 (13%)	7 (3%)	1 (<1%)
Metabolism and Nutrition Disorders	89 (20%)	12 (3%)	[illegible]	44 (21%)	6 (3%)	0
Musculoskeletal and Connective Tissue Disorders	98 (22%)	16 (4%)	[illegible]	44 (21%)	8 (4%)	0
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	5 (1%)	1 (<1%)	2 (<1%)	2 (1%)	1 (<1%)	1 (<1%)
Nervous System Disorder	190 (43%)	83 (19%)	3 (1%)	75 (36%)	42 (20%)	0
Psychiatric Disorders	108 (25%)	16 (4%)	0	38 (18%)	6 (3%)	[illegible]
Renal and Urinary Disorders	42 (10%)	0	0	8 (4%)	3 (1%)	0
Reproductive System and Breast Disorders	8 (2%)	0	0	3 (1%)		0
Skin and Subcutaneous Tissue Disorders	104 (24%)	0	0	32 (15%)	1 (<1%)	0
Surgical and Medical Procedures	2 (<1%)	0	0	2 (1%)	0	0
Vascular Disorders	48 (11%)	16 (4%)	1 (<1%)	19 (9%)	10 (5%)	3 (1%)

Patients treated with Optune/TMZ experienced a small increase in TMZ related AEs and SAEs due to the longer TMZ exposure afforded to these patients by their longer PFS. The only AEs which may have been caused by Optune therapy are the known skin irritation seen in 45% of patients in this study (1% severe), falls which were seen at a slightly higher incidence in patients carrying the device, headaches related to wearing the arrays 24 hours a day and mild psychiatric symptoms (anxiety, insomnia, confusion) which could be caused by the need to incorporate the device and arrays into daily life. No SAEs were considered related to device use. The remainder of AEs and SAEs seen in the trial were well balanced between treatment arms. In conclusion, Optune is very well tolerated with mild to moderate toxicity mainly related to array contact with the scalp.

Conclusions: Optune is a portable, battery operated device which delivers TTFields to patients with recurrent diagnosed GBM. The results of the pivotal trial in newly diagnosed GBM showed that Optune/TMZ extends progression free and overall survival significantly compared to patients receiving TMZ alone. No significant increase in adverse events is seen when Optune treatment is added to TMZ. The only common device-related AE was a skin irritation seen beneath the transducer arrays in 45% percent of patients. The majority (44 of 45%) of these events were mild to moderate. Based on an assessment of the Quality of life of the interim analysis cohort of 315 patients, cognitive function and functional status did not decline due to the use of Optune/TMZ.

RECURRENT DIAGNOSED GLIOBLASTOMA

Pilot Clinical Study in Recurrent GBM

Optune has been tested in 10 recurrent GBM subjects in a single center, pilot study in Europe. In this study, Optune monotherapy led to a significant increase in time to progression (from 13 to 26 weeks; p=0.013), progression free survival at 6 months (PFS6) (from 15 to 50%) and overall survival (OS) (from 6.0 to 14.7 months; p=0.002) compared to matched concomitant and historical comparator groups. The only device related adverse event (AE) seen in this trial was a mild to moderate skin irritation beneath the device transducer arrays.

Other Clinical Experience in Recurrent GBM

The Patient Registry Dataset (PRiDe) is a post-marketing registry of all recurrent GBM patients who received Optune in a real world, clinical practice setting in the US between 2011 and 2013. The registry included 457 recurrent GBM patients who received Optune in 91 US cancer centers. More patients in PRiDe than the pivotal clinical trial in recurrent GBM (EF-11) received Optune for first recurrence (33% vs. 9%) and had received prior bevacizumab therapy (55.1% vs. 19%). Median OS was significantly longer with Optune in clinical practice (PRiDe data set) than in the EF-11 pivotal trial in recurrent GBM (9.6 vs. 6.6 months). One- and 2-year OS rates were more than double for NovoTTF Therapy patients in PRiDe than in the EF-11 trial (1-year: 44% vs. 20%; 2-year: 30% vs. 9%). Favorable prognostic factors included first and second vs. third and subsequent recurrences, high Karnofsky Performance Score (KPS) and no prior bevacizumab use. No unexpected adverse events were detected in PRiDe. As in the EF-11 trial, the most frequent adverse events were mild to moderate skin reactions associated with application of the Optune transducer arrays.

Pivotal Clinical Study in Recurrent GBM[1]

Study Design: The study was a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of recurrent GBM subjects treated with Optune to those treated with an effective best standard of care (BSC) chemotherapy (including bevacizumab).

The following were the objectives of the study:

- To prospectively compare the median overall survival of recurrent GBM subjects treated with Optune to those treated with best standard of care (BSC) active chemotherapy
- To prospectively determine PFS6, TTP, %1-year survival and quality of life of subjects treated with Optune compared to BSC
- To collect evidence of the safety of TTFields applied to subjects with recurrent GBM using Optune

Eligibility Criteria: The inclusion and exclusion criteria for the trial were as follows

Inclusion Criteria

a. Pathological evidence of GBM using WHO classification criteria
b. ≥ 18 years of age
c. Not a candidate for further radiotherapy or additional resection of residual tumor
d. Subjects with disease progression (by Macdonald criteria (i.e. > 25% or new lesion)) documented by CT or MRI within 4 weeks prior to enrollment
e. Karnofsky scale ≥ 70
f. Life expectancy at least 3 months
g. Participants of childbearing age must use effective contraception
h. All subjects must sign written informed consent

Exclusion Criteria

a. Actively participating in another clinical treatment trial
b. Within 4 weeks from surgery for recurrence
c. Within 4 weeks from any prior chemotherapy
d. Within 4 weeks from radiation therapy
e. Pregnant
f. Significant co-morbidities within 4 weeks prior to enrollment:
   1) Significant liver function impairment AST or ALT > 3 times the upper limit of normal
   2) Total bilirubin > upper limit of normal
   3) Significant renal impairment (serum creatinine > 1.7 mg/dL)
   4) Coagulopathy (as evidenced by PT or APTT >1.5 times control in subjects not undergoing anticoagulation)
   5) Thrombocytopenia (platelet count < 100 x 103/μL)
   6) Neutropenia (absolute neutrophil count < 1 x 103/μL)
   7) Anemia (Hb < 10 g/L)
   8) Severe acute infection
g. Implanted pacemaker, defibrillator or deep brain stimulator, or documented clinically significant arrhythmias
h. Infra-tentorial tumor
i. Evidence of increased intracranial pressure (midline shift > 5mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)

[1] Stupp, R. et al. (2012) NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. Eur J Cancer 48(14): 2192-202

Study Procedures:

Treatment Arm

At treatment initiation subjects were hospitalized for 24 hours. During this period baseline examinations were performed and Optune treatment was initiated by the investigator under continuous medical supervision. The subjects were also instructed by the investigator on the operation of Optune and battery replacement. Once the subjects were trained in operating the device they were released to continue treatment at home. The subjects received continuous Optune treatment. Treatment was discontinued in the case of non-compliance or clinical disease progression.

Control Arm

All subjects had baseline examinations performed prior to treatment initiation. Subjects received the best effective standard of care chemotherapy practiced at each of the participating centers. The effective BSC treatments used in the study were comprised mainly of the following chemotherapies: Platinum based chemotherapy (Carboplatin), Nitrosureas (BCNU), Procarbazine, lomustine and vincristine (PCV), TMZ, Bevacizumab, and Imatinib, erlotinib, irinotecan (mainly in Europe). Because these therapies were included in the trial as a group, no comparisons can be made to each individual chemotherapy regimen. Chemotherapeutic treatment protocol was according to standard procedures at each of the participating centers.

Follow-up

During treatment, and until progression for subjects who stopped treatment before progression, all subjects were seen once a month at an outpatient clinic where they underwent medical follow up and routine laboratory exams. An MRI was performed every 2 months until disease progression. Central MRI review was performed by a neuro radiologist blinded to the treatment group of each subject. Medical follow-up continued for 2 months following disease progression. Subject survival was assessed based on monthly telephone interviews with the subjects' caregivers.

Subject Characteristics: 237 subjects (120 Optune; 117 BSC) with progressive or recurrent GBM were enrolled in the study. Baseline characteristics were as follows: mean age: 53.6 years; mean Karnofsky score: 81.6±10.9%, tumor size (cm²): 16.2±12.4; progression number: 1.4±0.9; re-operated: 26%; male: 70%; previous low grade: 10%; prior bevacizumab failure: 19%. Baseline characteristics were similar between treatment groups with slightly more men in the Optune group than in the BSC group (77% vs. 62%), a lower incidence of frontal lobe tumors in the Optune group than in the BSC group (32% vs. 50%), and a slightly higher mean KPS in the Optune group than in the BSC group (83% vs. 80%), though the median KPS was 80 in both groups. Adjusted analyses for all pre-specified or all statistically significant baseline covariates for overall survival did not change the outcome of the trial.

Demographics and Baseline Characteristics (ITT)

Characteristics	Optune (N=120) n (%)	BSC (N=117) n (%)
Caucasian	111 (93)	106 (91)
African American	2 (2)	5 (4)
Asian	0	3 (3)
Hispanic	7 (6)	2 (2)
Other	0	1 (1)
Female Gender	28 (23)	44 (38)
Frontal Tumor Position	38 (32)	58 (50)
Bilateral or Midline Tumor Location	23 (19)	17 (15)
Prior Avastin Use	24 (20)	21 (18)
Re-operation for Recurrence	33 (28)	29 (25)
Prior Low-grade Glioma	12 (10)	11 (9)
Median Age (years) (min, max)	54 (24, 80)	54 (29, 74)
Median Weight (kg)	90	80
Mean Number of Prior GBM Recurrences	1.5	1.3
Median Karnofsky Performance Score (min, max)	88 (50, 100)	80 (50, 100)
Median Tumor Area (mm²)	1440	1391
Median Time from GBM Diagnosis to Randomization (days)	334	340
Mean Time from Last Radiotherapy Dose to Randomization (Months)	13.71	13.93

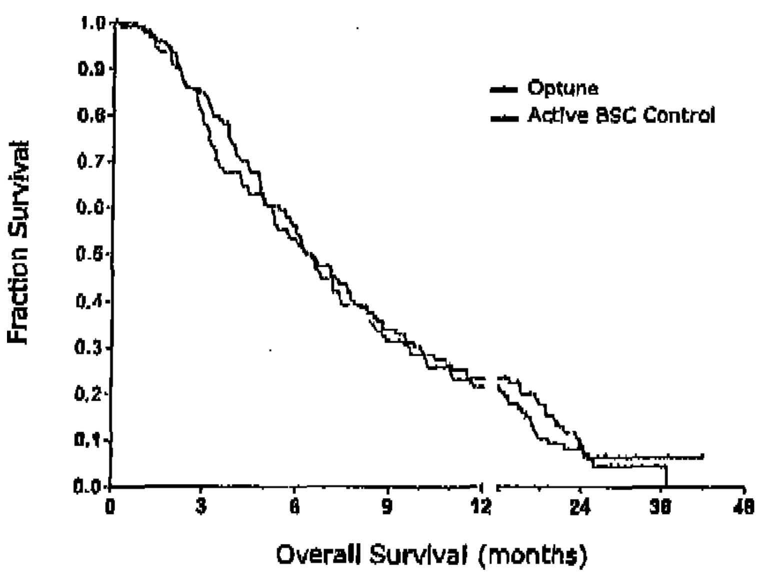
Effectiveness Results:

Primary Effectiveness Endpoint: Overall Survival (ITT)

In the ITT population which included all randomized subjects (Novo-TTF=120, BSC=117), overall survival in subjects treated with Optune was comparable to that observed in subjects treated with BSC (median OS=6.3 vs. 6.4 months; p=0.98). In the US, the median overall survival was 6.1 vs. 5.3 months in the ITT population. The pivotal study data establish that Optune therapy is comparable to BSC therapy in extending OS.

	Treatment Group	
	Optune	BSC
N	120	117
Median OS (months)	6.3	6.4
Log-rank p-Value	0.98	
Hazard Ratio (95% CI)	1.00 (0.76-1.32)	

The Kaplan-Meier survival curve for the two treatment groups appeared to be very similar during the first 12 months of follow-up, where 80% of the events occurred in both groups. Between 12 and 24 months, the survival curves separated slightly in favor of the BSC control group. However after 12 months, the number of subjects remaining may be too small to reliably estimate the long term survival outcome.



	Optune (N=120)	Active BSC Control (N=117)
Deaths	105	97
Censored	15	20
Lost to follow-up	6	10
Alive at end of follow-up	9	10
Median (months)	6.3	6.4
95% Confidence Interval	5.6, 7.8	5.2, 7.4

Correlation between Treatment Compliance and Overall Survival: Optune has an internal log file which allows the calculation of patient compliance with treatment. Significantly higher overall survival (p=0.0447) was observed in patients who were treated 75% or more of the time on average (OS=7.7 months) compared to patients treated less than 75% of the time on average (OS=4.5 months).

Secondary Effectiveness Endpoints: Secondary endpoint results support the findings in the primary endpoint. The one-year survival is similar in the Optune and BSC groups in the ITT population (21.9% vs. 22.1%). Progression free survival at 6 months (PFS6) is the same in the ITT population (21.4% vs. 15.2%). Radiological response rates from the subset of patients evaluated were reported as 14% for the Optune group compared to 9.6% for the BSC group in the ITT population. Median time to progression (TTP) was 9.3 weeks for Optune vs. 9.6 weeks for BSC.

	Treatment Group	
	Optune	**BSC**
N	120	117
1-year survival	21.9% 25/114	22.1% 23/104
PFS6 (%)	21.4% 22/103	15.2% 14/92
Radiological Response Rate (%)	14.0% 14/100	9.6% 7/73
Median TTP (weeks)	9.3	9.6

Quality of Life: Quality of life in subjects using Optune was better than those on BSC chemotherapy in most subscale domains, including vomiting, nausea, pain, diarrhea, constipation, cognitive and emotional functioning.

Safety Results: The characteristic adverse events of almost all chemotherapies are seen in a significantly higher proportion of BSC control subjects than in Optune subjects: gastrointestinal (30% vs. 8%), hematological (19% vs. 4%) and infectious (12% vs. 4%). Mild to moderate skin irritation beneath the device transducer arrays was observed in 16% of Optune subjects; none of these cases were assessed as severe by the investigator, all resolved after discontinuing treatment, and all were treated with topical steroids and periodic shifting of transducer array positions.

Number of Patients with Adverse Events by Body System (>2%)

System Organ Class	Optune	BSC Chemotherapy
	N=116 (%)	N=91 (%)
Blood and lymphatic disorders	5 (4.3%)	17 (18.7%)
Gastrointestinal disorders	9 (7.8%)	27 (29.7%)
General disorders and administration site conditions	15 (12.9%)	14 (15.4%)
Infections and Infestations	5 (4.3%)	11 (12.1%)
Injury, poisoning and procedural complications	21 (18.1%)	1 (1.1%)
Metabolism and nutrition disorders	9 (7.8%)	12 (13.2%)
Nervous system disorders	50 (43.1%)	33 (36.3%)
Psychiatric disorders	12 (10.3%)	7 (7.7%)
Respiratory, thoracic and mediastinal disorders	7 (6.0%)	10 (11.0%)

Conclusions: Optune is a portable, battery operated device which delivers TTFields to patients with recurrent GBM. The results of the pivotal trial showed that Optune subjects had comparable overall survival to subjects receiving the best available chemotherapy in the US today (OS 6.3 vs. 6.4 months; HR 1.0; p=0.98). Similar results showing comparability of Optune to BSC chemotherapy in the ITT population were seen in all secondary endpoints.

Optune subjects experienced fewer adverse events in general, significantly fewer treatment related adverse events, and significantly lower gastrointestinal, hematological and infectious adverse events compared to BSC controls. The only device-related adverse event seen was a mild to moderate skin irritation beneath the device transducer arrays, which was easily treated with topical ointments. Finally, certain quality of life measures were better in Optune subjects as a group when compared to subjects receiving effective BSC chemotherapy.

Directions for Use

Detailed directions for use for Optune can be found in.
The Optune Patient Information and Operation Manual

Abbreviations

AE – Adverse event

BSC – Best standard of care (effective chemotherapies)

GBM – Glioblastoma Multiforme (Glioblastoma, Astrocytoma grade IV), the most common and anaplastic primary brain tumor

ITT – Intent-to-Treat. This analysis population includes all randomized subjects.

kHz – kilo hertz; number of cycles per second

Optune– A portable battery, or power supply, operated device for delivering 200 kHz TTFields to the brain of patients with recurrent GBM

OS – Overall survival

PP – Per Protocol. This analysis population includes all patients who received at least the first course of TMZ and had no major protocol deviations.

PFS – Progression free survival

PFS6 – Proportion of patients alive and progression free at 6 months from randomization

Radiological Response Rate - sum of complete and partial radiological response rates

TMZ – a type of cancer drug used to treat newly diagnosed GBM

TTFields – Tumor Treating Fields: Low intensity (1-3 V/cm), Intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated transducer arrays to the region of the body inflicted with a solid tumor. The fields have been shown in vitro to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase

TTP – Time to progression

V/cm – Volts per centimeter; the unit of intensity measurement of electric fields

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SNO

The Society for NeuroOncology

A multidisciplinary organization for the advancement of neuro-oncology through research and education

The following abstract will be presented on Saturday, November 15, 2014, at 11:40am at the 19th Annual Scientific Meeting of the Society for Neuro-Oncology. The information below is embargoed until 8:00am, Saturday, November 15, 2014.

Interim Analysis of the EF-14 Trial: A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM

Roger Stupp, Eric Wang, Charles Scott, Sophie Taillibert, Andrew Kanner, Santosh Kesari and Zvi Ram on behalf of the EF-14 Trial Investigators

BACKGROUND: Tumor Treating Fields (TTFields) are an anti-mitotic, physical treatment modality that acts in metaphase, anaphase and telophase. The NovoTTF-100A System (NovoTTF), a home-use medical device that delivers TTFields to the brain, is an established monotherapy for recurrent glioblastoma (GBM).

METHODS: We conducted an international, multicenter, prospective, randomized phase III trial in newly diagnosed GBM patients. After completion of radiotherapy (RT) with concomitant temozolomide (TMZ), patients were randomized (2:1) to adjuvant TMZ with NovoTTF or adjuvant TMZ alone. The primary endpoint was progression-free survival (PFS), with overall survival (OS) an important secondary endpoint. Here we report on a pre-specified interim analysis of the first 315 patients randomized, after a minimum follow-up of 18 months (range 18-60 months).

RESULTS: (intent-to-treat): 210 pts were randomized to NovoTTF/TMZ and 105 to TMZ alone. Patient characteristics were balanced: median age 57 and 58 years, tumor resection in 89 and 90%, KPS 90%, for the NovoTTF and the control arms, respectively. *MGMT* promoter methylation status was assessable centrally in 60% of patients; of these 39% and 41% were methylated. Adverse events (AE) were comparable between treatment arms. The most common device-related AE was skin irritation in 45% of patients (all grades, severe 2%). Severe seizures were observed at a frequency of 7% in both arms. Median PFS was 7.1 months (mo) (95% confidence interval [CI] 5.9-8.2) and 4.0 mo (CI 3.0-4.3; Hazard ratio 0.63, p=0.001), OS was 19.6 mo (CI 16.5.-24.1) and 16.6 mo (CI 13.5-19.1) (HR 0.75, p=0.034), both favoring NovoTTF. This translates into a 24-mo survival rate of 43% (CI 36-50%) and 29% (CI 21-39%) for the NovoTFF/TMZ and the TMZ alone arm, respectively.

CONCLUSIONS: The trial met its primary and main secondary endpoints, and was closed to accrual after this interim analysis. Adjuvant TMZ chemotherapy and NovoTTF provides a clinically and statistically significant improvement in progression-free and overall survival, and should become the new standard of care against GBM.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
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Baltimore, Maryland 21244-1850

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES
CENTER FOR MEDICARE

Center for Medicare
Refer to: FCHBE

JUL 26 2013

James C. Stansel
Sidley Austin LLP
1501 K Street, NW
Washington, DC 20005

Dear Mr. Stansel:

Thank you for your inquiry requesting an informal benefit category determination (BCD) for the NovoTTF™-100A System.

According to your letter and the information you provided during the meeting with Centers for Medicare and Medicaid Services (CMS) on May 21, 2013, the NovoTTF™-100A System is a non-invasive system used in the patient's home that delivers tumor treating fields therapy to the brain to disrupt rapid cell division exhibited by recurrent GMB tumors. The NovoTTF™-100A System is comprised of a durable electrical field generator and disposable insulated transducer arrays for use with the Generator. The System also includes lithium ion batteries, battery rack, battery charger, power supply, connection cables, and a carrying case. The NovoTTF™-100A System received pre-market approval (PMA) from FDA in April 2011 for recurrent GBM.

In order for an item to be covered by Medicare, it must meet the definition of a Medicare-covered benefit. However, it is important to note that although Medicare provides coverage for certain items, it does not provide coverage for every item that may be useful to a person with a medical problem, even if a physician prescribes the item. The Medicare definition of durable medical equipment (DME) includes equipment which: can withstand repeated use; has an expected life of at least three years; is primarily and customarily used to serve a medical purpose; generally is not useful to a person in the absence of an illness or injury; and is appropriate for use in the home.

Based on the product information we reviewed, we believe that the NovoTTF™-100A System falls within the DME benefit category. I hope that this information is helpful to you.

Sincerely,

Joel E. Kaiser
Director
Division of DMEPOS Policy

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OPTUNE™

(FORMERLY NOVOTTF™-100A SYSTEM)

CLINICAL DOSSIER

TUMOR TREATING FIELDS THERAPY

Treatment for Glioblastoma Multiforme

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List of Abbreviations and Definitions of Terms

AE – Adverse Event

BCNU – Carmustine, chemotherapy

BPC – Best Physician Choice

BSC – Best Standard Care

c – Centigrade

CCNU – Lomustine (CeeNU), chemotherapy

CE Mark -- Conformité Européene mark, for products sold in the European Economic Area

CI – Confidence Interval

cm -- Centimeters

DTIC -- Dacarbazine

dAEs -- Dermatologic adverse events

ECG -- Electrocardiogram

EMC -- Electromagnetic Compatibility

F-98 – Rat glioblastoma cell line

FDA -- Food and Drug Administration

GBM – Glioblastoma Multiforme (Glioblastoma, Astrocytoma grade IV), the most common and anaplastic primary brain tumor

Gy – Gray, unit of radiation

HR -- Hazard Ratio

ITT -- Intent-to-Treat

INE – Insulated Electrical Array

kHz – Kilo Hertz; number of cycles per second

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KPS – Karnofsky Scale

mHz -- Mega Hertz, number of cycles per second

MGMT -- 06-methylguanine-DNA methyltransferase

mITT -- Modified intention-to-treat

mo. -- Months

MRI -- Magnetic Resonance Imaging

ORR - Objective Response Rate

OS – Overall Survival

PCV – Procarbazine, CCNU and vincristine-combination chemotherapy

PFS – Progression Free Survival

PFS6 – Progression Free Survival at 6 months

PMA – Pre-market Approval

PRiDe -- Patient Registry Dataset

QOL – Quality of Life

RR – Radiological Response Rate--Sum of complete and partial radiological response rates

TENS -- Transcutaneous Electrical Nerve Stimulation

TMZ--Temozolomide

TTFields – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated transducer arrays to the region of the body inflicted with a solid tumor. The fields have been shown to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase.

U-87 - Human glioblastoma cell line

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US – United States

V/cm -- Volts per centimeter; the unit of intensity measurement of electric fields

WHO -- World Health Organization

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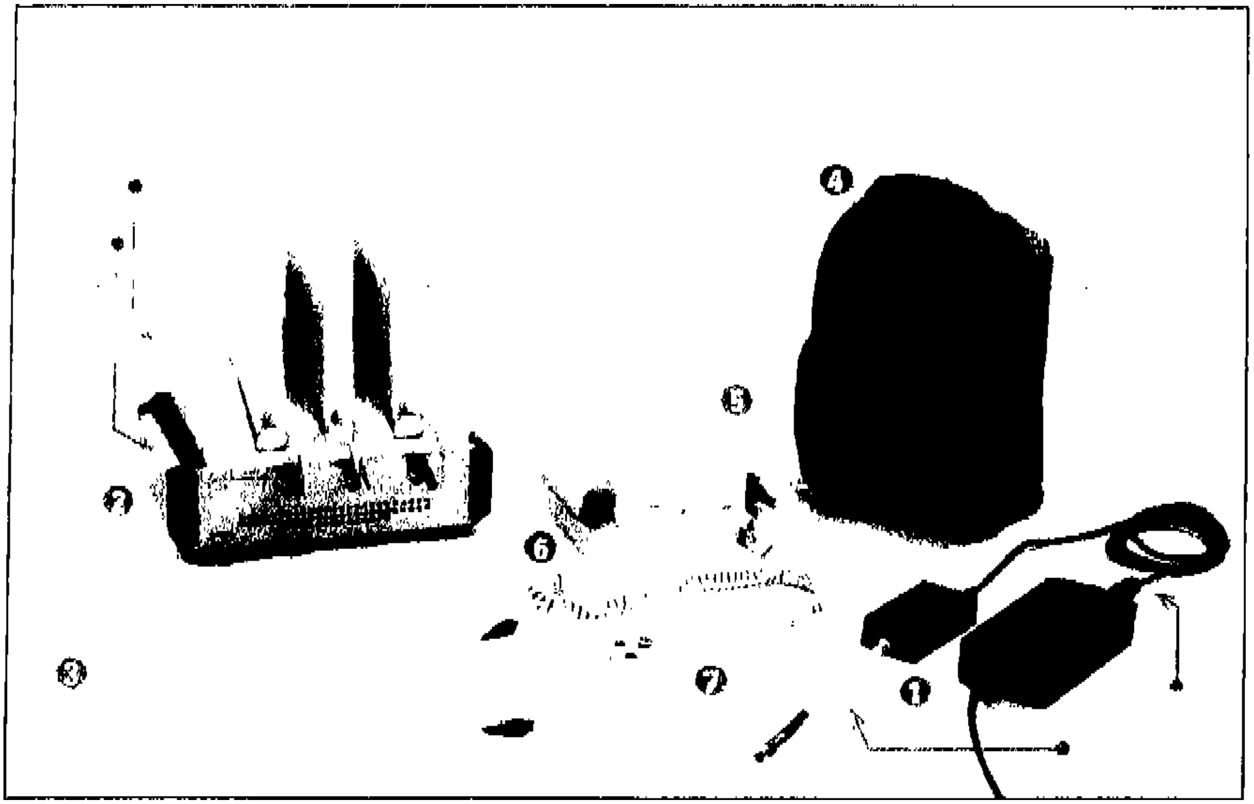
Figure 1. Optune Treatment Kit



1 Plug In Power Supply

2 Charger for Portable Batteries

3 Transducer Arrays

4 Device & Battery Carrying Bag

5 Electric Field Generator (the Device)

6 Portable Battery

7 Connection Cable & Box

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Figure 2. Use of Device Overview

1. Prepare scalp.

2. Remove four transducer arrays from package.

3. Place transducer arrays on scalp.

4. Connect transducer arrays to connection cable & device. Match colored rings to color coded sockets.

5. Place device and battery in bag (if applicable) and connect battery or power supply.

6. Connect connection cable to device.

7. Start treatment. Turn on power switch and push TTFields button.

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8. Place bag over shoulder.

9. Replace transducer arrays as needed.

10. Recharge batteries when not in use.

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1] Burden of Illness and Standard of Care for GBM

Glioblastoma multiforme (GBM), a malignant form of astrocytoma, is the most common and most aggressive form of primary brain cancer; but it remains a rare disease.

Burden of Illness

The incidence of GBM increases steadily above 45 years of age, with approximately 10,000 new cases annually in the United States. GBM tends to occur more frequently in males than females by a ratio of about 3:2. The outcome of patients with this disease has not improved significantly in recent years, despite the introduction of improved chemotherapies, including temozolomide (TMZ) (Merck; Temodar), bevacizumab (Roche, Avastin), and the use of GLIADEL® Wafers (carmustine). The 4-year survival of these patients is only 6.3% with a median overall survival (OS) of 14.6 months (Ostrom, 2015).

Nearly all patients with newly diagnosed GBM relapse within the first year despite aggressive treatment. Recurrent GBM is an end-stage condition; median OS from time of recurrence is approximately 3 to 5 months without additional effective treatment.

Quality of Life (QOL) for patients with GBM is generally poor due to the neurological deficits caused by the tumor itself together with the associated side effects of the various approved and experimental treatments.

Insurance Burden

To determine which US health insurers cover GBM patients, it is helpful to know that the median age at diagnosis is approximately 64 years Therefore, the expected population for a private health care payer in the US is approximately 16 patients per 1 million covered lives (10,000 with GBM x 50% non-Medicare x 64% with private health care coverage = 3,200 divided by 201.1 million covered lives with private insurance = 16 lives per million covered).

Existing Treatment Options for GBM

There are currently four principal treatment options for GBM. Even with these treatments, the median time to recurrence of the tumor has been extended by only a few months. Once the tumor has recurred, patients have limited treatment options.

Newly Diagnosed GBM

Standard of care for a patient with newly diagnosed GBM and adequate functional status is debulking surgery, radiation with concurrent TMZ followed by adjuvant TMZ. Some elderly patients simply receive standard radiation or TMZ. Any or all of the following options may be pursued:

- **Surgical Resection** – Surgery to debulk the tumor and obtain tissue for diagnosis is the most common initial approach for newly diagnosed GBM. The surgical goal is to remove as much of the tumor as possible without

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compromising neurological function. When surgical resection is not feasible due to tumor location or patient's clinical condition, open or stereotactic biopsy may be performed.

- **GLIADEL® Wafer in Combination with Surgical Resection** – The GLIADEL® Wafer may be placed in the brain cavity at the time of surgical resection to deliver carmustine (BCNU) directly to the site of the brain tumor (interstitial chemotherapy). A modest increase in median survival has been shown over placebo (13.9 mo. vs. 11.6 mo.) when used in newly diagnosed GBM. Treatment with GLIADEL® wafer is associated with the following common side effects (incidence >10% and between arm difference ≥4%): cerebral edema, asthenia, nausea, vomiting, constipation, wound healing abnormalities and depression.

- **Radiation Therapy – Localized radiotherapy is typically** given over a six-week period following surgical resection with a total dose of approximately 60 grays (Gy). Side effects of radiation therapy depend on the type of radiation received, the amount of the surface of the brain targeted, the site targeted, and the total dose of radiation. In general, there will be hair loss, skin irritation, possible hearing problems, nausea, vomiting, loss of appetite, and neurologic effects. The most prevalent side effect is fatigue, which may last through treatment and for many months afterwards.

- **Cytotoxic Chemotherapy** – TMZ, an oral alkylating agent, is administered concomitant with radiation therapy and continued for a minimum of six months following radiation. Significantly improved OS and median survival have been demonstrated in large trials. Recent studies have shown that patients with methylated 06-methylguanine-DNA methyltransferase (MGMT) may have a superior response to TMZ therapy. Side effects from TMZ therapy include: nausea, vomiting, loss of appetite, constipation, tiredness, and headache. Temporary loss of hair also can be expected.

Recurrent GBM

There is little data on effective strategies for treatment of recurrent GBM.

- **Surgical Resection** – Repeat surgery for GBM at the time of tumor recurrence may be offered when it is feasible although there is no data indicating that it offers significant survival benefit. Second surgery is considered in only about 20% of patients.

- **GLIADEL® Wafer In Combination with Surgical Resection** – Use of GLIADEL® Wafer is limited to selected cases undergoing additional surgical resection for recurrent GBM. The package insert indicates that for recurrent GBM, GLIADEL® Wafer increased median OS from 4.6 to 6.5 months compared to placebo.

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- **Radiation Therapy** - Because the full standard dose of radiation (60 Gy) typically is given after initial diagnosis with GBM, irradiation for disease recurrence may not be possible. However, with advances in technology, re-irradiation with fractionated stereotactic radiotherapy can provide survival benefit.

- **Cytotoxic Chemotherapy** - There is no established standard treatment for recurrent GBM. Chemotherapy treatment strategies are ill-defined, with several different preferred regimens. The most common are: nitrosureas, (BCNU), procarbazine, PCV (procarbazine, CCNU and vincristine), and platinum based (e.g. carboplatin). None of these agents is FDA approved specifically for recurrent GBM. Most patients suffer from combinations of unpleasant and sometimes life-threatening side effects of their chemotherapeutic treatments,

- **Bevacizumab (Avastin)** may be used as monotherapy for patients with recurrent GBM (Cohen, 2009). The FDA approval was based on two phase 2, single arm trials comparing bevacizumab to historical control data. Benefit was seen in objective response (OR) rates and progression free survival at six month (PFS6) compared to historical control data. OS was shown to be between 8 to 9 months however, an OS claim is not made in the approved labeling

In summary, despite an aggressive initial standard of therapy treatment, most GBM patients develop recurrent disease. When tumors recur, only 20% of patients are eligible for additional resection. There is a high unmet need for therapies to treat recurrent GBM.

2] Description and Use of Optune

Overview
Optune is a portable, wearable medical device, which produces alternating electrical fields, tumor treating fields or "TTFields," within the brain by means of electrically-insulated surface transducer arrays placed on the scalp. The TTFields are believed to disrupt the rapid cell division exhibited by cancer cells.

Indication for Use:
Optune™ is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme. (GBM)

Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy

For the treatment of recurrent GBM, Optune™ is indicated following histologically-or radiologically-confirmed recurrence in the supratentorial region of the brain after

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receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options

Summary of Important Safety Information:

Contraindications
Do not use Optune if you have an active implanted medical device, a skull defect (such as, missing bone with no replacement), or bullet fragments. Use of Optune together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune ineffective.

Do not use Optune if you are known to be sensitive to conductive hydrogels. In this case, skin contact with the gel used with Optune may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings and Precautions
Use Optune only after receiving training from qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by Novocure (the device manufacturer).

Do not use Optune if you are pregnant, you think you might be pregnant or are trying to get pregnant. It is not known if Optune is safe or effective in these populations.

The most common (≥10%) adverse events involving Optune in combination with temozolomide were low blood platelet count, nausea, constipation, vomiting, fatigue, scalp irritation from device use, headache, convulsions, and depression.
The most common (≥10%) adverse events seen when using Optune alone were scalp irritation from device use and headache.

The following adverse reactions were considered related to Optune when using the device alone: scalp irritation from device use, headache, malaise, muscle twitching, fall and skin ulcer.

All servicing procedures must be performed by qualified and trained personnel.

Do not use any parts that do not come with the Optune Treatment Kit, or that were not sent to you by the device manufacturer or given to you by your doctor.

Do not wet the device or transducer arrays.

If you have an underlying serious skin condition on the scalp, discuss with your doctor whether this may prevent or temporarily interfere with Optune treatment.

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System Components
Optune is comprised of two main components: 1) an Electric Field Generator (the "device") and 2) INE Insulated Transducer Arrays (the "arrays"). (See **Figure 1** for illustration.)

- The device is portable, battery- or power supply-operated. It is connected to two pairs of array sets, which operate sequentially. The intensity of the field, the frequency of the waves, and the temperature of the transducer arrays are pre-set and monitored by the device. The device and battery weigh about six pounds together.

- The transducer arrays are disposable and approved for single use only. They are highly engineered, using military grade insulation that cannot withstand repeated use due to micro-cracks that form over time. The arrays are embedded with a precise temperature sensing technology to prevent skin burns. They are designed to deliver and monitor the therapy simultaneously while maintaining electrical insulation and patient safety. Due to their advanced engineering requirements and unique material composition, they contribute meaningfully to the device cost.

Additional Components: In addition to the device and transducer arrays, the Optune treatment kit includes a plug-in power supply, portable batteries, battery charger, connection cable, and carrying case. (See **Figure 1** for illustration.)

Treatment Overview
Overview
The US FDA requires that the treating physician complete training and receive certification from the manufacturer prior to prescribing treatment with Optune. Additionally, nurses, nurse practitioners, physician's assistants, and any other health care professional providing direct patient care related to Optune must also have completed training and certification.

The manufacturer-provided training is designed to educate the prescribing physician and allied healthcare professionals on the scientific basis for Optune therapy, clinical information on the efficacy and safety of Optune, the process to interpret an MRI to determine the array layout plan, the training required for the patient, and also the steps to start and oversee treatment, including the process of assessing monthly compliance.

Transducer Array Layout Plan
The physician must plan the appropriate layout of the transducer arrays around the tumor location prior to starting treatment. This layout planning process requires a current patient MRI. Treatment planning determines the appropriate array placement to maximize Optune intensity within the tumor.

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Treatment Start

Treatment initiation often takes place in the patient home. The patient and caregiver receive device related training from a Novocure representative. The patient has his or her scalp shaved to ensure proper contact of the transducer arrays to the skin. The caregiver places the arrays in accordance with the prescribed array layout and initiates therapy by turning the device on. (See **Figure 2** for illustration.)

Patient and Caregiver Training

Novocure representatives are responsible for training the patient and caregiver on the technical aspects and use of the device. All medical questions are referred back to patient's provider. This training involves technical training related to the device operation, including educating the patient on battery replacement, battery charging, using the power supply, connecting and disconnecting from the device, and on the appropriate placement of transducer arrays in accordance with the treatment plan. Additionally, the patient and caregiver will have access to a 24-hour technical support service offered by the device manufacturer.

Transducer Array Placements – After Successful Patient Training

The patient and caregiver, once properly trained, are expected to change the transducer arrays. The caregiver will be trained to shave the patient's scalp, maintain good skin care protocols, and to place the arrays in accordance with the prescribed treatment plan. The arrays are changed and the scalp is re-shaved about every three to four days to ensure contact with the skin. Patients know to change the arrays when the alarm beeps more often to signal the need for the change.

Monthly Treatment Assessment

Patients typically are scheduled to meet the physician once per month, exclusive of Optune treatment. The Novocure Representative will provide the physician a monthly compliance report which is reviewed with the patient during this appointment. The compliance log provides the physician with an overview of device usage by day and by time of day (day versus night). The physician uses this compliance log to encourage appropriate use of Optune. During this monthly appointment, the physician also reviews transducer array location to ensure appropriate placement in accordance with the prescribed treatment plan. If compliance is problematic, patients and caregivers may be retrained in the proper use of the device.

Device Use Overview

Treatment Duration

The physician-prescribed device is used for newly diagnosed patients in combination with temozolomide and as monotherapy for patients diagnosed with recurrent glioblastoma. Physicians may choose to keep patients on Optune at first recurrence. For maximum benefit, the recommended average daily use is at least 18 hours a day.

Device Settings

Novocure pre-sets all device treatment parameters; there are no programming adjustments available to the patient. The patient simply connects the device to an

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appropriate power supply (i.e., a charged battery or connection of the power supply to an electrical outlet) and turns it on and off.

Practical Considerations

Treatment may be interrupted for personal needs such as bathing or exercise. In order to take a shower, the patient must disconnect from the device (leaving the transducer arrays on the head), put on a shower cap, and be cautious not to get his/her head or any components of the device wet. Treatment also must be stopped to replace the arrays. When leaving the house, patients can put a wig or hat over the arrays, if desired.

Device Service

The device and batteries require frequent servicing. Novocure provides the patient with replacements for these components, as needed, and in most cases ships on an overnight basis. For minor technical issues, an alarm will sound to notify the patient. The patient manual has a simple troubleshooting guide that addresses the most common problems that may arise. In addition, Novocure has around-the-clock technical support. Patients are encouraged to call the Novocure technical support telephone number with questions about operations or device function.

FDA Approvals

The US Food and Drug Administration (FDA) approved Optune for use in newly diagnosed GBM in October 2015. (See FDA Approval Letter, **Appendix A**.)

Optune has been available for use in recurrent GBM since FDA approval (via premarket approval (PMA) pathway) in April 2011. (See FDA Approval Letter, Appendix A.)

Regulatory Approval Outside the United States

Optune is a CE Marked (Conformité Européene) device cleared for sale in the European Union, Switzerland, Australia, Israel and Japan.

3] Optune Mechanism of Action

Background

The Optune System delivers tumor treating fields (TTFields) to the tumor. TTFields are intended to disrupt cancer cell division by utilizing the unique electrical and geometric properties of cells during the mitotic process.

Electric fields traditionally have been used in medicine in two different modes: 1) steady or low frequency electric fields (<1 kHz); and 2) high frequency alternating fields (>10 mHz). Steady or low frequency electric fields generate action potentials in excitable cells. These fields are used therapeutically in bone and soft tissue repair, pain control (TENS), and stimulation (neurologic or cardiac). In contrast, very high frequency

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alternating fields generate heat in the tissues by dielectric losses. Applications in therapeutic use include ablation, diathermy and hyperthermia.

In contrast, Optune harnesses intermediate frequency (200 kHz), low intensity (1-3 V/cm), alternating electric fields) to achieve its therapeutic effect. At this frequency and intensity, Optune cannot stimulate nerves or muscles or bone growth, nor do they heat the tumor or surrounding tissues. Since Optune is applied using electrically insulated arrays, there is no direct current flow into the tissue hence electrolysis and tissue damage do not occur. TTFields are delivered non-invasively via the arrays to GBM tumors using the Optune device.

Mechanism of Action

TTFields target two specific characteristics of cancer cells: the presence of electrically charged particles during mitosis and the geometrical shape of dividing cancer cells. TTFields have been shown to:

- inhibit cancer cell replication by interference with the proper formation of the mitotic spindle during metaphase and anaphase; and

- cause intracellular dielectrophoesis of macromolecule and organelles during cytokinesis.

Acting together, these two processes, which are specific to dividing cells only, may lead to apoptosis and can result in tumor arrest or regression *in vivo*.

In contrast, data indicate that Optune does not affect cells that are quiescent, that is, that are not dividing. Since most normal adult brain cells proliferate very slowly, if at all, scientists hypothesize that these cells are affected minimally by Optune. Additionally, the antimitotic effect of Optune has been shown to be frequency-specific to the cell type treated.

Optune application has the advantage of being locally-directed and is not expected to be associated with systemic toxicity.

4] Summary of Clinical Studies

Pilot and pivotal studies in both newly diagnosed and recurrent GBM have demonstrated that Optune is safe and effective in patients with GBM. The most recently completed study, EF-14 in newly diagnosed GBM, compared Optune in combination with maintenance TMZ compared to TMZ alone. The previous EF-11 trial for recurrent GBM compared Optune alone with best physician choice chemotherapy (BPC). To date, Optune therapy has been used in more than 2500 patients in the clinical as well as commercial setting. What follows is a synopsis of the EF-14 pivotal trial in newly

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diagnosed GBM and a summary of the published clinical study literature for both indications.

Newly Diagnosed GBM

A] EF-14 Pivotal Study

Overview

The EF-14 trial, as reported by Stupp et al. 2015, was a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of newly diagnosed GBM subjects treated with Optune and TMZ to those treated with TMZ alone. The multicenter, multinational (83 global centers) trial had a medium follow-up of 38 months (range 18 to 60 mo.). Sixty-one percent of study patients were from the US. Study endpoints were as follows:

Primary Endpoint: Progression-free survival (PFS) in the intent-to-treat population assessed by an independent review panel (significance threshold of .01)

Secondary Endpoint: Overall survival (OS) in the per-protocol (PP) population (significance threshold of .006)

Study Population

Patients with histologically confirmed GBM were recruited to the trial after completing maximal safe debulking surgery or biopsy , followed by radio-therapy in combination with TMZ chemotherapy.

Eligibility Criteria

Inclusion Criteria

- *Pathological evidence of GBM using World Health Organization (WHO) classification criteria*
- *≥18 years of age*
- *Received maximal debulking surgery and radiotherapy (45-70Gy) concomitant with TMZ*
- *Karnofsky scale ≥ 70*
- *Life expectancy at least 3 months*
- *Participants of childbearing age must use effective contraception.*
- *All patients must sign written informed consent.*
- *Treatment start date at least 4 weeks out from surgery.*
- *Treatment start date at least 4 weeks out but not more than 7 weeks from the later of last dose of concomitant TMZ.*
- *Treatment start date at least 4 weeks out from radiation therapy*

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Exclusion Criteria

- *Progressive disease (according to MacDonald Criteria[1]).*
- *Actively participating in another clinical treatment trial*
- *Pregnant*
- *Significant co-morbidities at baseline which would prevent maintenance TMZ treatment:*
  - *Thrombocytopenia (platelet count < 100 x $10^3/\mu L$)*
  - *Neutropenia (absolute neutrophil count < 1.5 x $10^9/\mu L$)*
  - *CTC grade 4 non-hematological Toxicity (except for alopecia, nausea, vomiting)*
  - *Significant liver function impairment - AST or ALT > 3 times the upper limit of normal*
  - *Total bilirubin > upper limit of normal*
  - *Significant renal impairment (serum creatinine > 1.7 mg/dL)*
- *Implanted pacemaker, defibrillator, deep brain stimulator, or documented clinically significant arrhythmia.*
- *Infra-tentorial tumor*
- *Evidence of increased intracranial pressure (midline shift > 5mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)*
- *History of hypersensitivity reaction to TMZ or a history of hypersensitivity to dacarbazine (DTIC).*

Study Procedure After completion of treatment with TMZ and radiotherapy, patients were randomized at a ratio of 2:1 to receive standard maintenance TMZ (150-200 mg/m /d for 5 days every 28 days for 6-12 cycles) with or without the addition of Optune. The web-based randomization was stratified by extent of resection and MGMT methylation status.

Treatment Arm: Optune was given together with maintenance TMZ. At treatment initiation, patients were seen at an outpatient clinic. During this visit, patients received baseline examinations and Optune treatment was initiated. The patients were instructed on the operation of Optune and battery replacement. Once the patients were trained in operating the device, they were released to continue treatment at home. Following radiological progression or unacceptable toxicity, TMZ could be replaced with BSC second line chemotherapy. However, Optune could be continued until the second radiological progression, or clinical deterioration, for a maximum of 24 months.

[1] The Macdonald criteria divides response into 4 types of response based on imaging (MRI) and clinical features: complete response; partial response; stable disease; progression.

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Control Arm: All subjects had baseline examinations performed prior to treatment initiation. Patients were treated with maintenance TMZ according to the standard dosing regimen. Following radiological progression or unacceptable toxicity, TMZ could be replaced with BSC second line therapy.

Follow Up: During treatment, all patients were seen once every month at an outpatient clinic where they underwent medical follow-up and routine laboratory exams. Treatment adherence with Optune was recorded by the device, then reviewed and transferred at follow-up visits. A magnetic resonance imaging (MRI) was performed every second month following the baseline MRI until second progression or 24 months (whichever came first), when treatment on both arms of the study was terminated. In the case of clinical progression, an unscheduled MRI was obtained within 1 week after the investigator became aware of the clinical progression. No additional MRIs were required after second progression. Central MRI review was performed by an independent radiologist blinded to the treatment group of each patient. Medical follow-up continued for 2 months after treatment termination in order to capture treatment related toxicities. After these visits, mortality was assessed based on monthly telephone interviews with the patients or the patients' caregivers.

Study Patients: The study enrolled 695 of the 700 planned patients between July 2009 and November 2014; Optune/TMZ (n = 466) or TMZ alone (n = 229). Data from the prespecified interim analysis of the first 315 patients with a minimum of 18 months of follow-up included 210 patients in the Optune plus TMZ arm and 105 in the TMZ alone arm. Baseline characteristics were well balanced in both groups. (See Appendix B) An independent data and safety monitoring committee review of the interim data determined that the predefined improvement in PFS and OS had been met and recommended termination of the study. Following FDA approval of the termination, the study was closed to recruitment and patients in the control group were allowed to crossover and receive Optune. A total of 35 patients crossed over. Follow-up for all patients continues; final analysis data are not expected before the end of 2016. The results that follow here are from the interim analysis.

Analysis Populations: PFS was analyzed in the intent-to-treat (ITT) population, which included all randomized subjects (Optune/TMZ--210; TMZ alone--105 at the interim analysis). OS was analyzed in the PP population which excluded all patients who 1) never started TMZ maintenance therapy, 2) had major protocol violations, 3) crossed over to the other treatment group, or 4) received Optune outside the protocol (Optune/TMZ=196; TMZ alone=84).

Treatment Delivery

The median number of TMZ cycles until evidence of first tumor progression was 6 cycles (range, 1-26 cycles) for patients in the Optune plus TMZ arm and 4 cycles (range, 1-24 months) in the TMZ arm alone. The median duration of treatment with Optune was 9 months (range, 1-58 months). Two-thirds of patients in the Optune plus TMZ arm continued treatment with TTFields after first tumor progression. Three-quarters of

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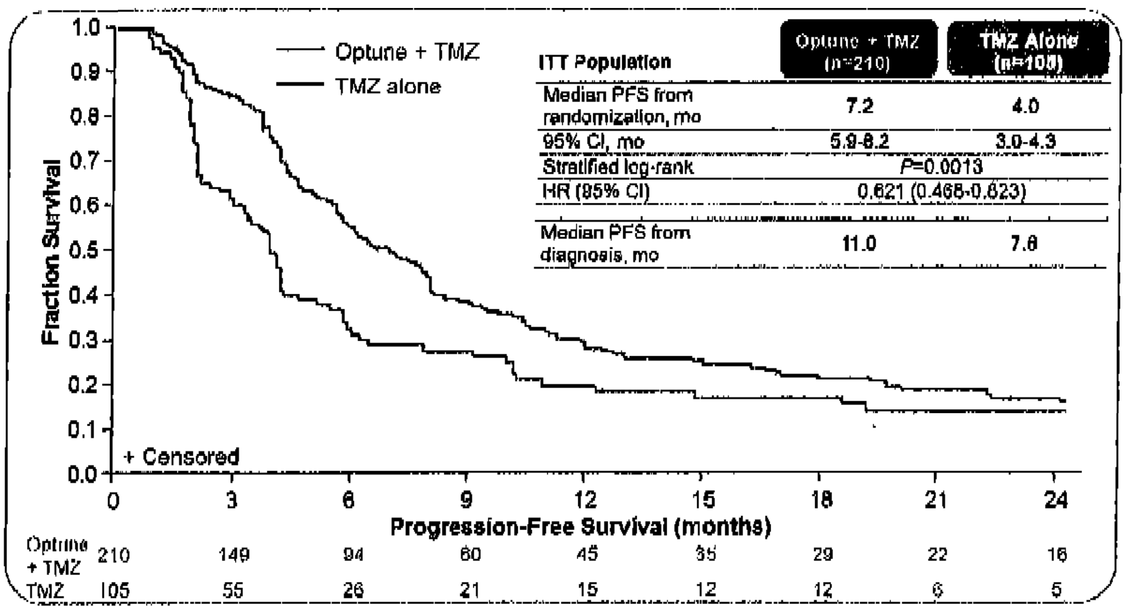
patients receiving Optune complied with therapy, wearing the device >18 hours per day on average for the first 3 treatment months.

Effectiveness Results:

Primary Effectiveness Endpoint: Progression Free Survival--ITT Population

The threshold for statistical significance of PFS at the interim analysis was pre-defined as an α level of .01 using a stratified log-rank test. PFS at the interim analysis met this threshold. After a median follow-up of 38 months (range, 18-60 months), the median PFS from randomization was 7.1 months (95% CI, 5.9-8.2 months) in the Optune plus TMZ arm compared with 4.0 months (95% CI, 3.3-5.2 months) in the TMZ only arm. Thus, the addition, of Optune to BSC TMZ extended median PFS by 3.1 months. (See Figure 3.)

Figure 3. Progression Free Survival: ITT Population



Secondary Effectiveness Endpoint: Overall Survival--PP population

OS was a powered secondary analysis in the trial and was to be tested only after the primary endpoint was found to surpass the threshold for significance in the interim analysis. The threshold for superior OS at the interim analysis was predefined in the protocol as an α level of .006 using a stratified log-rank test and was to be tested in the PP population (Optune/ TMZ = 196, TMZ alone = 84). Median OS in the PP population was 20.5 months (95%CI, 16.7-25.0 months) in the Optune plus TMZ arm compared with 15.6 months (95%CI, 13.3-19.1 months) in the TMZ alone arm.

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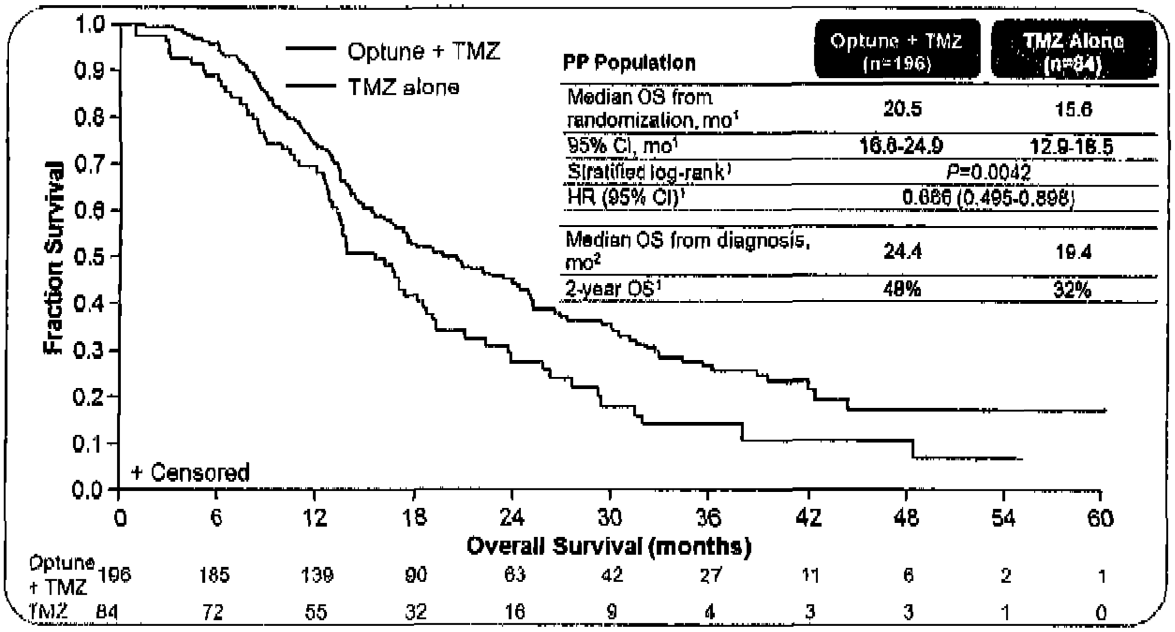
Figure 4. Overall Survival: PP Population



In an additional survival analysis of the ITT population, median OS was 19.6 months (95% CI, 16.6-24.4 months) in the Optune plus TMZ arm compared with 16.6 months (95% CI, 13.6-19.2 months) in the TMZ alone arm. Further, the percentage of patients alive at 2 years following enrollment was 43% in the Optune plus TMZ arm compared with 29% in the TMZ alone arm.

Robustness Analysis: To assess the robustness of the interim analysis findings, additional analyses on all 695 patients randomized were performed. Baseline characteristics of all patients randomized were similar to the interim data set as were the results for the main endpoints. PFS in the ITT population was 7.1 months (95% CI, 6.1-8.13 months) for the Optune plus TMZ arm and 4.2 months (95% CI, 3.93-5.87 months for the TMZ alone arm. OS in the ITT population also favored Optune treated patients with a median of 19.4 months (95% CI, 16.6-23.9 months) vs. 16.6 months (95% CI, 13.9-18.6 months).

Safety Results: The addition of Optune to TMZ in patients with newly diagnosed GBM was not associated with any significant increase in systemic toxic effects compared with TMZ alone. (See **Appendix C**) However, patients receiving Optune did experience a higher incidence of localized skin toxicity (medical device reaction beneath the transducer arrays). Mild to moderate skin irritation was observed in 43% of patients treated with Optune plus TMZ and severe skin reaction (grade 3) noted in 2%. Skin reactions could be managed by using published skin care guidelines for patients receiving Optune. Mild anxiety, confusion, insomnia and headaches were reported more frequently in patients treated with Optune plus TMZ and occurred mainly at the time of therapy initiation. The incidence of seizures was 7% for the Optune plus TMZ arm and

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8% in the TMZ alone arm. Twelve patients died of causes considered to be unrelated to treatment, 8 (3.9%) in the Optune plus TMZ arm and 4 (4.0%) in the TMZ alone arm.

Conclusions: Results of the interim analysis of the pivotal trial in newly diagnosed GBM show that Optune plus TMZ significantly extends PFS and OS compared to patients receiving TMZ alone. The addition of Optune to BSC TMZ was shown to be safe; no significant increase in serious AEs was seen when Optune treatment was added to TMZ. The most common (≥10%) adverse events involving Optune in combination with TMZ were low blood platelet count, nausea, constipation, vomiting, fatigue, scalp irritation from device use, headache, convulsions, and depression.

Recurrent GBM

B] EF-11 Pivotal Study

Stupp et al. (2012) published data from the EF-11 trial, a prospective, multicenter, randomized, active controlled clinical trial designed to compare the safety and effectiveness outcomes of recurrent GBM patients treated with Optune to those treated with BPC chemotherapy (including bevacizumab) selected by the treating physician. A total of 237 patients were enrolled in the study from 28 clinical centers in the US and Europe. The final study analysis compared 120 Optune patients with 117 BPC chemotherapy patients.

The study objectives were:

- To prospectively compare the OS of recurrent GBM patients treated with Optune to those treated with BPC chemotherapy.
- To prospectively determine the median survival, percent one-year survival rate, PFS, PFS6, RR rate and QOL of patients treated with the Optune compared to BPC chemotherapy.
- To collect evidence of the safety of Optune for patients with recurrent GBM using Optune.

Patients with previously diagnosed GBM who had relapsed or progressed despite conventional therapy (surgery and chemo-radiotherapy followed by chemotherapy) were recruited into the study. More than 80% of patients had failed two or more prior lines of chemotherapy and 20% had failed bevacizumab prior to enrollment, a population that usually fares poorly with subsequent treatments. Patients in the treatment arm received continuous Optune treatment at home while maintaining normal daily activity. Chemotherapy treatments used in the control arm were comprised mainly of the following as single agents or in combination: bevacizumab (Avastin) or irinotecan

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(mainly in Europe) followed by nitrosureas (BCNU), platinum based chemotherapy (carboplatin), and TMZ. Patients were seen monthly and had an MRI every two months until disease progression. Mean use of Optune was 20.6 hours per day.

Study results are summarized below.

- The pivotal study data establish that Optune therapy is at least comparable to chemotherapy in extending OS for patients with recurrent GBM; 6.6 months vs. 6.0 months.

- The secondary effectiveness endpoint results support the findings of the primary endpoint; they show the Optune device is at least clinically equivalent to active chemotherapy. In summary: PFS for treatment arm was 2.2 mo. vs. 2.1 mo.; PFS6 was 21.4% vs. 15.1%; and radiological response rate (RR) rate was 14.0% vs. 9.6%.

- QOL for patients treated with Optune is significantly improved compared to patients treated with active chemotherapies. Patients in the study arm reported improved cognitive, emotional and role functioning, and a marked improvement in adverse treatment-related symptoms such as nausea and pain.

- In a clinical trial, Optune was shown to be safe and well tolerated with significantly less toxicity than existing treatment options for recurrent GBM. The most common (≥10%) adverse events seen when using Optune alone were scalp irritation from device use and headache. The following adverse reactions were considered related to Optune when using the device alone: scalp irritation from device use, headache, malaise, muscle twitching, fall and skin ulcer.

Conclusion: The pivotal study data established that Optune produces clinically comparable outcomes to BPC chemotherapy, including bevacizumab (Roche; Avastin), across both primary OS and secondary effectiveness end-points for recurrent GBM patients. Additionally, Optune therapy results in fewer treatment related adverse events and certain QOL measures were better with Optune than compared to BSC chemotherapy.

C] Patient Registry Dataset (PRiDe)

Mrugala et al (2014) report on PRiDe a post-marketing registry of patients who received Optune Therapy for recurrent GBM in the U.S. between October 2011 and November 2013. Data were collected from all 457 recurrent GBM patients who began commercial treatment during that period. Age and gender characteristics were similar in the PRiDe and EF-11 trial. OS was collected using the Social Security Death Date Registry and obituaries. Subgroup analyses were performed on patient/clinical characteristics and found to be significantly correlated with OS . A monthly compliance assessment was

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performed for each patient using a computer download of an internal log file from the Optune device.

Study findings include the following:

- Median OS for those on Optune therapy was significantly longer in PRiDe than in the EF-11 trial (9.6 mo. vs. 6.6 mo.)
- One- and two-year OS rates for Optune therapy patients were more than double in PRiDe as compared to the EF-11 trial (1-year- 44% vs. 20%; 2-year- 30% vs. 9%).
- No new adverse events were detected in PRiDe. The most common device-related adverse event was a skin irritation beneath the transducer arrays, easily treated with topical corticosteroids.

Major median OS differences in patients registered in PRiDe compared to median OS of those treated with Optune monotherapy in the EF-11 trial led to subgroup analyses to explore reasons for the variation. These analyses suggest there may be several favorable prognostic factors that influence OS in Optune–treated patients. These include: daily compliance ≥75%, Optune therapy initiated at first recurrence, use in Bevacizumab naïve patients , and KPS ≥90.

Conclusion: Understanding favorable prognostic factors may assist in appropriate patient selection for Optune

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Appendix A

FDA Approval Letters

Newly Diagnosed GBM
http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013a.pdf

Recurrent GBM
http://www.accessdata.fda.gov/cdrh_docs/pdf10/p100034a.pdf

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Appendix B

EF-14 Pivotal Trial Interim Analysis Patient Characteristics

ITT Population **Characteristics**	Optune + TMZ (n=210)	TMZ Alone (n=105)
Median age, years (range)	57 (20-83)	58 (21-80)
Female sex, n (%)	70 (33)	38 (36)
Median KPS (range)	90 (60-100)	90 (70-100)
Extent of resection, n (%)		
Gross total resection	135 (64)	67 (64)
Partial resection	52 (25)	27 (26)
Biopsy	23 (11)	11(10)
MGMT status, n (%)		
Methylated	49 (23)	26 (25)
Unmethylated	79 (38)	38 (36)
Insufficient for testing	24 (11)	11 (10)
Not assessed	58 (28)	30 (29)
Median time from diagnosis to randomization, mo (range)	3.8 (2.0-5.7)	3.8 (1.4-5.7)
Duration of Therapy		
Median number of TMZ cycles, n (range)	6.0 (1-26)	4.0 (1-24)
Median number of Optune cycles, n (range)	9.0 (1-58)	0 (0-0)

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Appendix C
Pivotal Trial Adverse Events—Interim Analysis Population

Safety Population System Organ Class	Optune + TMZ (n=437) n (%)	TMZ Alone (n=207) n (%)
Blood and lymphatic system disorders		
Thrombocytopenia	32 (7)	10 (5)
Leukopenia	8 (2)	1 (<1)
Lymphopenia	14 (3)	7 (3)
Neutropenia	8 (2)	3 (1)
Anemia	5 (1)	4 (2)
General disorders and administration site conditions		
Fatigue	15 (3)	7 (3)
Asthenia	7 (2)	1 (<1)
Procedural complications		
Fall	8 (2)	1 (<1)
Nervous system disorders		
Headache	10 (2)	3 (1)
Convulsion	19 (4)	11 (5)
Cognitive disorder	4 (1)	4 (2)
Hemiparesis	9 (2)	1 (<1)
Brain edema	9 (2)	6 (3)
Cerebral hemorrhage	0 (0)	4 (2)
Respiratory disorders		
Pulmonary embolism	8 (2)	7 (3)

- The most common (≥10%) adverse events involving Optune in combination with TMZ were thrombocytopenia, nausea, constipation, vomiting, fatigue, medical device site reaction, headache, convulsions, and depression

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Clinical Practice Experience With NovoTTF-100A™ System for Glioblastoma: The Patient Registry Dataset (PRiDe)

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Recurrent glioblastoma multiforme (GBM) is a highly aggressive cancer with poor prognosis, and an overall survival of 6 to 7 months with optimal therapies. The NovoTTF-100A™ System is a novel antimitotic cancer therapy recently approved for the treatment of recurrent GBM, based on phase III (EF-11) trial results. The Patient Registry Dataset (PRiDe) is a post-marketing registry of all recurrent GBM patients who received NovoTTF Therapy in a real-world, clinical practice setting in the United States between 2011 and 2013. Data were collected from all adult patients with recurrent GBM who began commercial NovoTTF Therapy in the United States between October 2011 and November 2013. All patients provided written consent before treatment was started. Overall survival (OS) curves were constructed for PRiDe using the Kaplan-Meier method. Median OS in PRiDe was compared for patients stratified by average daily compliance (≥75% *v* <75% per day) and other prognostic variables. Adverse events were also evaluated. Data from 457 recurrent GBM patients who received NovoTTF Therapy in 91 US cancer centers were analyzed. More patients in PRiDe than the EF-11 trial received NovoTTF Therapy for first recurrence (33% *v* 9%) and had received prior bevacizumab therapy (55.1% *v* 19%). Median OS was significantly longer with NovoTTF Therapy in clinical practice (PRiDe data set) than in the EF-11 trial (9.6 *v* 6.6 months). One- and 2-year OS rates were more than double for NovoTTF Therapy patients in PRiDe than in the EF-11 trial (1-year: 44% *v* 20%; 2-year: 30% *v* 9%). First and second versus third and subsequent recurrences, high Karnofsky performance status (KPS), and no prior bevacizumab use were favorable prognostic factors. No unexpected adverse event was detected in PRiDe. As in the EF-11 trial, the most frequent

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0093-7754/ - see front matter

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adverse events were mild to moderate skin reactions associated with application of the NovoTTF Therapy transducer arrays. Results from PRIDe, together with those previously reported in the EF-11 trial, indicate that NovoTTF Therapy offers clinical benefit to patients with recurrent GBM. NovoTTF Therapy has high patient tolerability and favorable safety profile in the real-world, clinical practice setting.

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Glioblastoma multiforme (GBM) is the most aggressive form of human glioma and accounts for approximately 60% to 70% of all malignant gliomas.[1,2] Based on data from the 2013 Central Brain Tumor Registry of the United States (CBTRUS) statistical report on primary brain and CNS tumors in the United States, an estimated 9,600 to 11,200 new cases of GBM will be diagnosed in 2014.[1,2] Virtually all patients with newly diagnosed GBM relapse despite maximal multimodality treatment,[3] with a median time to recurrence of approximately 7 months.[4] The prognosis for patients with recurrent GBM is even worse. The median progression-free survival (PFS) was only 9 weeks in the pre-bevacizumab era.[5] In 2009, bevacizumab received accelerated approval from the US Food and Drug Administration (FDA) for the treatment for recurrent GBM based on two single-arm studies with favorable response rates and PFS data.[1,6,7] Formal phase III data is not available in the recurrent setting, however phase III comparison of bevacizumab versus placebo in newly diagnosed glioblastoma patients failed to demonstrate prolongation of survival with bevacizumab.[1,8] A major challenge in treatment of recurrent GBM, particularly with bevacizumab, is that the tumor eventually develops resistance to the drug. Moreover, bevacizumab-treated tumors may convert to a more aggressive phenotype histologically and exhibit infiltrative tumor growth as observed on magnetic resonance imaging (MRI).[9,10] Furthermore, patients with recurrent GBM who progress following bevacizumab therapy are typically resistant to subsequent cytotoxic chemotherapies.[1,11,12] Therefore, new treatments that can offer a different mechanism of action and potentially overcome resistance of GBM are desperately needed.

The NovoTTF-100A™ System (Novocure, Ltd., Haifa, Israel) is a novel antimitotic cancer therapy approved in 2011 by the US FDA for the treatment of recurrent supratentorial GBM,[13,14] based on the results of a phase III trial comparing NovoTTF Therapy with best chemotherapy according to physician choice.[15] The unique mechanism of action of NovoTTF Therapy involves localized delivery of alternating low-intensity, intermediate-frequency, tumor-treating fields (TTFields) via non-invasive transducer arrays attached to the patient's scalp.[14] In preclinical studies, TTFields have been shown to selectively kill or arrest the growth of rapidly dividing cancer cells including glioblastoma cell lines by disrupting both mitotic spindle formation and normal cytokinesis by interrupting cytoplasmic furrow formation.[16–20]

The pivotal phase III (EF-11) trial that led to FDA approval of the device compared NovoTTF Therapy (n = 120) with best chemotherapy according to physician's choice (n = 117) in recurrent GBM patients from 28 institutions in seven countries.[15] More than 80% of patients in the study had failed two or more prior chemotherapies, and 20% had experienced recurrence while on bevacizumab. Seventy-eight percent of the 116 patients who started NovoTTF Therapy completed at least one full-treatment course (4 weeks). The results demonstrated comparable median OS with NovoTTF Therapy compared with chemotherapy (6.6 *v* 6.0 months; hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.66 to 1.12; $P = .27$), together with fewer severe adverse events (6% *v* 16%, $P = .022$) and improved quality-of-life measures for the NovoTTF Therapy arm compared with chemotherapy. The most common adverse events with NovoTTF Therapy were mild to moderate skin irritation associated with the transducer arrays. Systemic adverse events commonly associated with chemotherapy were generally absent in patients receiving NovoTTF Therapy.

Given the mechanism of action of TTFields and the results of preclinical studies, optimal device compliance is required for therapeutic effectiveness with NovoTTF Therapy. NovoTTF Therapy does not have a half-life, therefore it requires continuous application to exert a therapeutic effect. This differs from systemic chemotherapy, which exerts anticancer effects between administrations due to the drug pharmacokinetics. Based on modeling of tumor growth kinetics and supporting preclinical and clinical data, NovoTTF Therapy must be administered almost "continuously" for at least 4 weeks in order to halt tumor growth and subsequently demonstrate an objective response.[21,22] Recommended administration of NovoTTF Therapy

is ≥18 hours per day for each 4-week treatment cycle.[21] A post hoc analysis of the phase III trial data recently showed significantly longer median OS in NovoTTF Therapy patients with a maximal monthly compliance rate ≥75% (≥18 hours daily) versus those with a <75% compliance rate (7.7 *v* 4.5 months, $P = .042$) (see Kanner in this supplement). A recent responder analysis also demonstrated very high compliance rates >90% in EF-11 responders.[23]

The Patient Registry DatasEt (PRiDe) is a registry of 457 recurrent GBM patients who received NovoTTF Therapy in the clinical practice setting on the US commercial prescription-use program between October 2011 and November 2013. Patients treated in clinical trials often differ from those who receive treatment in the real-world setting due to patient selection criteria and frequently represent a less homogenous group. Hence registry data can be an important source of additional information about the efficacy and safety of a newly approved therapy. This report analyzes data from PRiDe to help us better understand the potential benefits of NovoTTF Therapy for patients with recurrent GBM, including analyses of median OS, tolerability, and the relationship between survival and compliance as well as other prognostic factors.

METHODS

Patients and Data Collection

PRiDe data were collected from all patients ≥18 years old with recurrent GBM who began commercial treatment with NovoTTF Therapy in the United States between October 2011 and November 2013. All participating patients provided written informed consent to use protected health information to advance the understanding of NovoTTF Therapy. Recurrent GBM was defined as histologically-confirmed, supratentorial GBM (World Health Organization grade IV astrocytoma) with radiologically confirmed evidence of disease progression, as defined by the Macdonald criteria,[24] following treatment with radiotherapy with or without concomitant and/or adjuvant chemotherapy. Patients who received NovoTTF Therapy were not restricted to the number or types of prior therapies or recurrences. Information about combination use of NovoTTF Therapy as part of the prescription-use program was not captured. Therefore some patients may have received combination therapy (chemotherapy or anti-vascular endothelial growth factor [VEGF] agents) rather than monotherapy.

Baseline characteristics were assessed by manual patient chart review. OS was collected using the Social Security Death Date Registry and obituaries. Novocure started collecting compliance data centrally in January 2013, so such data are only available for under two thirds of patients in the registry. A monthly compliance assessment was performed for each patient by computer download of an internal log file which captures the cumulative amount of time therapy is delivered to the patient. Patient compliance was calculated as the average percentage of each day the system was delivering fields (out of each 24-hour period). In addition, other prognostic factors, such as the number of prior recurrences, age, KPS, prior bevacizumab use, and any debulking surgery were captured and analyzed. Adverse events were recorded prospectively according to National Cancer Institute Common Toxicity Criteria. Quality-of-life measures were not assessed in PRiDe.

Statistical Analysis

The OS and treatment duration curves were constructed using the Kaplan-Meier method. OS in PRiDe was compared to OS for patients receiving NovoTTF Therapy or best chemotherapy in the phase III EF-11 trial (ITT population) using a log-rank (Mantel-Cox) test. Patient or disease characteristics prognostic for survival with NovoTTF Therapy were assessed using a Cox proportional hazards model (P value of .15 for significant interactions). Subgroup analyses were performed on patient/clinical characteristics found to be significantly correlated with OS. A log-rank test was used to compare the relationship between OS and daily compliance (<75% *v* ≥75%), prior debulking surgery (yes, no), KPS (90–100, 70–80, 10–60), recurrence number (1st, 2nd, 3rd–5th recurrence) and prior bevacizumab use (prior use *v* naïve).

RESULTS

Patient Characteristics

Four-hundred fifty-seven patients with recurrent GBM were treated with NovoTTF Therapy between October 2011 and November 2013 at 91 oncology centers. This population is more than three times the 120 subjects treated with NovoTTF monotherapy, as well as the 117 subjects treated with chemotherapy, in the phase III EF-11 trial, from which we were making a comparison. Baseline patient characteristics are presented in Table 1. Patient characteristics T1 (age and gender) were generally similar in PRiDe and the two treatment groups in the EF-11 trial. Approximately one third of patients treated commercially with NovoTTF Therapy were women, which is an important observation given the perceived cosmetic considerations of head shaving and array placement.

Table 1. Baseline Patients and Clinical Characteristics for Patients With Recurrent Glioblastoma Multiforme in PRIDe and EF-11 Trial

Characteristic		PRiDe NovoTTF Therapy (n = 457)	EF-11 NovoTTF Therapy (n = 120)	EF-11 Chemotherapy (n = 117)
Age (y)	Median (range)	55 (18–86)	54 (24–80)	54 (29–74)
Gender	Male	67.6%	77%	62%
	Female	32.4%	23%	38%
KPS	Median (range)	80 (10–100)	80 (50–100)	80 (50–100)
	10–60	19.0%	NA	NA
	70–80	46.6%	NA	NA
	90–100	30.9%	NA	NA
	Unknown	3.5%	NA	NA
Recurrence	Median (range)	2 (1–5)	2 (1–5)	2 (1–4)
	First	33.3%	9%	15%
	Second	26.9%	48%	46%
	Third to Fifth	27.4%	43%	39%
	Unknown	12.5%	0%	0%
Prior treatments	Bevacizumab	55.1%	19%	18%
	RT + temozolomide	77.9%	86%	82%
	Debulking surgery	63.9%	79%	85%
	Carmustine wafers	3.7%	NA	NA

Abbreviations. KPS, Karnofsky performance status; NA, not applicable; RT, radiotherapy.

Tolerability and Safety

No new adverse events were detected in PRiDe compared to those found in EF-11. The most common device-related adverse events associated with NovoTTF Therapy in the registry were skin reactions/irritation and heat sensations on the scalp beneath the transducer arrays (Table 2). Patients sometimes described these events as "warmth" or "tingling" sensations, none of which were associated with injury to the patient. Systemic adverse events, which were often associated with chemotherapy (eg, gastrointestinal, hematologic, and infectious adverse events), were rare for patients treated with NovoTTF Therapy in the registry.

Survival Rates

Figure 1 presents Kaplan-Meier curves of OS for patients treated with NovoTTF Therapy in the clinical practice setting (PRiDe) and those who received NovoTTF Therapy or best chemotherapy as part of the EF-11 trial (ITT population). Median OS on NovoTTF Therapy appeared to be markedly longer in PRiDe than in the EF-11 trial (9.6 *v* 6.6 months). Median OS was also significantly longer with NovoTTF Therapy in PRiDe than with best chemotherapy group in the EF-11 trial (9.6 *v* 6.0 months). One- and 2-year OS rates for NovoTTF Therapy patients in PRiDe were more than double those seen with either NovoTTF Therapy or best chemotherapy in the EF-11 trial (Table 3).

Median treatment duration for patients in PRiDe was 4.1 months (95% CI, 3.5–4.8). In comparison, the median treatment duration in the EF-11 study was 2.3 months (95% CI, 2.1– 2.4) for NovoTTF Therapy arm and 2.1 months (95% CI, 2.0–2.9) for best chemotherapy. Figure 2 shows the fraction of NovoTTF Therapy patients still on treatment over time. Roughly 50% were still on NovoTTF Therapy after 4 months from treatment start, and roughly 10% were still on NovoTTF Therapy at 2 years after treatment start.

Compliance as a Prognostic Factor and Its Relationship to OS

Because of the major difference in the OS in patients registered in PRiDe as compared to the OS of subjects treated with NovoTTF monotherapy in EF-11, we sought to identify the prognostic factors in the former cohort. The first prognostic factor we analyzed was NovoTTF treatment compliance because it was found to be prognostically important in EF-11 in post hoc analysis. Compliance data was collected centrally starting in January 2013 and, therefore, were only available for 287 of the 457 patients (63%) in the registry. The median daily compliance was 70% for patients treated with NovoTTF Therapy in PRiDe (range, 12%–99%). One

Table 2. Adverse Events in Patients With Recurrent Glioblastoma Multiforme Treated With NovoTTF Therapy in PRiDe

Adverse event	Percentage of Patients PRiDe (n = 457)
Skin reaction	24.3
Heat sensation	11.3
Neurological disorder	10.4
Seizure	8.9
Electric sensation	7.7
Headache	5.7
Pain/discomfort	4.7
Fall	3.9
Psychiatric disorder	2.9
Gastrointestinal disorder	2.9
Fatigue	2.5
Vascular disorder	1.6
Weakness	1.4
Infections	1.4
Eye disorder	1.3

hundred twenty-seven (44%) with available data achieved daily compliance of ≥75% of each day, while 160 (56%) had daily compliance of <75%. As illustrated in Figure 3, median OS was significantly longer in patients with a NovoTTF Therapy daily compliance ≥75% than in those with <75% daily compliance (13.5% *v* 4.0%; HR, 0.43; 95% CI, 0.29–0.63; *P* <.0001).

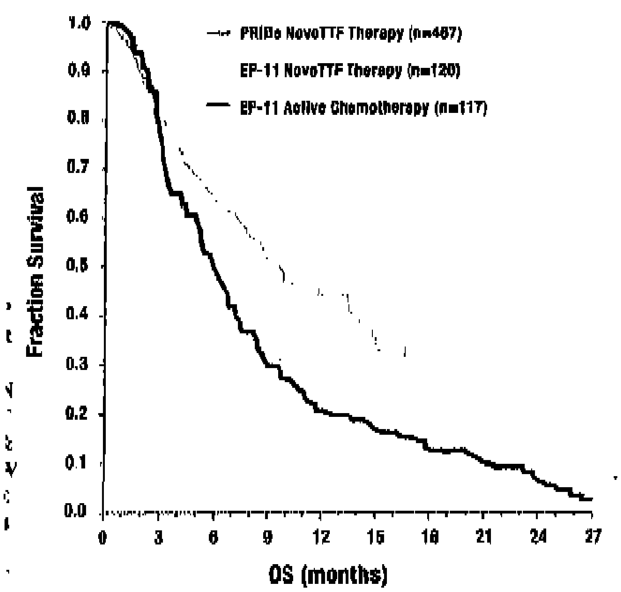

Figure 1. Kaplan-Meier overall survival (OS) curves for patients with recurrent glioblastoma multiforme treated with NovoTTF Therapy in PRiDe or with NovoTTF Therapy or best chemotherapy in the EF-11 trial.

Other Prognostic Factors

The Cox proportional hazards model identified the presence or absence of debulking surgery, number of prior recurrences, compliance, KPS, and prior bevacizumab therapy as significant independent predictors of OS in patients treated with NovoTTF Therapy in PRiDe (*P* <.15). Table 4 presents log-rank OS testing between patient subgroups in PRiDe for each of these prognostic factors; Figure 4 presents Kaplan-Meier survival curves for these same factors. First, no difference in median OS was observed between patients who did not have surgical debulking and those who did (8.9 *v* 9.8, respectively; HR, 1.1; 95% CI, 0.8–1.5; *P* = .7927). Second, recurrent GBM patients treated with NovoTTF Therapy in clinical practice at their first recurrence experienced a significantly longer median OS as compared to patients treated at their second, third, or subsequent recurrence (20 months compared to 8.5 and 4.9 months, respectively; HR, 0.6; 95% CI, 0.4–0.9; p = 0.0271 and HR, 0.3; 95% CI, 0.2–0.5; *P* <.0001). It should be noted that a greater percentage of patients in PRiDe were at their first GBM recurrence compared with patients treated with NovoTTF Therapy or best chemotherapy in the EF-11 trial (33.3% *v* 9% and 15%, respectively). In addition, differences were also apparent between patients in PRiDe and those in the EF-11 trial with respect to prior treatments. More than half of NovoTTF Therapy patients in PRiDe had previously received bevacizumab (55.1%), compared with only 19% of NovoTTF monotherapy and 18% of best active chemotherapy cohorts in the EF-11 trial. Third, recurrent GBM patients with KPS ≥90 experienced a near doubling of median OS compared with patients with a KPS of 70–80, median OS 14.8 versus 7.7 months, respectively, HR 0.6 (95% CI, 0.4–0.9), *P* = .0070. Lastly, the survival of bevacizumab-naïve patients was significantly longer compared to patients who had received prior bevacizumab before starting NovoTTF Therapy, with a respective median OS 13.4 versus 7.2 months, HR 0.5 (95% CI, 0.4–0.7), *P* <.0001. These data suggest

Table 3. One- and 2-Year Survival Rates for Patients With Recurrent Glioblastoma Multiforme Treated With NovoTTF Therapy in PRiDe and EF-11 trial, and With Best Chemotherapy in the EF-11 Trial

Endpoint	PRiDe NovoTTF Therapy (n = 457)	EF-11 NovoTTF Therapy (n = 120)	EF-11 Chemotherapy (n = 117)
1-Year survival	44%	20%	20%
2-Year survival	30%	9%	7%

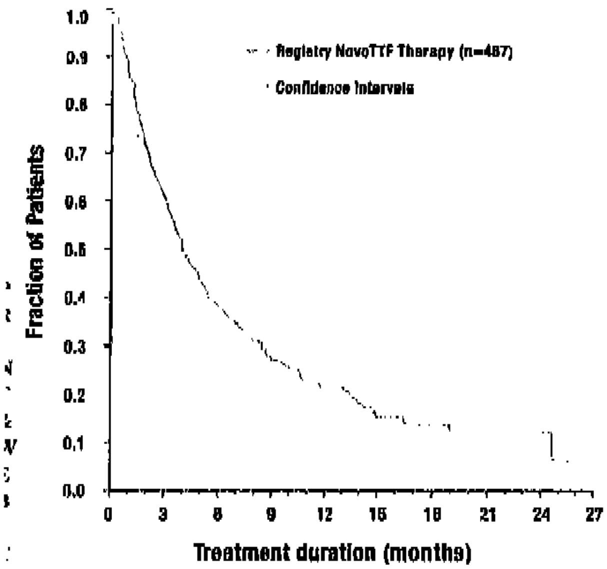

Figure 2. Fraction of NovoTTF Therapy patients alive by treatment duration (PRiDe).

that, within this heterogeneous group of patients registered in PRiDe, there were many patients who derived significant benefit from NovoTTF Therapy.

DISCUSSION

The Patient Registry Dataset, or PRiDe, represents 457 unselected patients with recurrent GBM who received NovoTTF Therapy in a real-world, clinical practice setting across 91 cancer centers in the United States between October 2011 and November 2013. No new, unexpected adverse event was detected with NovoTTF Therapy in this cohort. Similar to those found in the EF-11 trial,[15] the most common adverse events associated with NovoTTF Therapy were mild to moderate skin reactions localized to the scalp beneath the transducer arrays. These reactions were easily treated with topical corticosteroids or antibiotics, were not associated with serious injury to the scalp, and typically did not require interruption of treatment. Some patients in PRiDe reported subjective sensations beneath the transducer arrays, often described as "warmth" or "tingling." These heat or electric sensations were captured as adverse events in PRiDe ("skin reaction"), but not in the EF-11 trial. These sensations occur when the contact between transducer arrays and the skin is suboptimal, and usually indicate the presence of hair regrowth. In these instances, re-shaving the head can re-establish optimal contact between the skin and transducer arrays. Furthermore, systemic adverse events commonly observed with chemotherapy were largely absent in patients treated with NovoTTF Therapy in PRiDe as they were in the EF-11 trial.[15]

Patients receiving NovoTTF Therapy for recurrent GBM demonstrated a median OS of 9.6 months in clinical practice. This compares favorably to the reported median OS for the EF-11 pivotal trial cohort treated with NovoTTF monotherapy, where median OS was 6.6 months, and to OS of patients who received treatments for recurrent GBM in other clinical trials.[25–28] For example, recent reports of median OS in recurrent GBM patients treated with bevacizumab are in the range of 6 to 10.5 months,[7,12,25–27,29] and those treated with temozolomide in the range 6 to 9 months.[30–32] It should be noted that many of the longer term survivals noted in clinical trials of bevacizumab and temozolomide in recurrent GBM included small sample sizes and none were randomized.

The difference between the OS seen in clinical practice and in the EF-11 trial may in part be due the greater percentage of patients with a first GBM recurrence in PRiDe versus patients in the EF-11 study (33.3% *v* 9%, respectively). This observation is also supported by a prior post hoc analysis of EF-11 that showed a significantly longer median OS in patients treated with NovoTTF Therapy at their first or second recurrence compared to those treated at third or subsequent recurrences. Furthermore, when used as intended (daily compliance ≥75% or ≥18 hours daily), the median OS for patients treated with NovoTTF Therapy in PRiDe was remarkably high at 13.5 months compared to only 4.0 months in those who had suboptimal compliance (daily compliance <75% or <18 hours daily). Kanner et al (see accompanying Kanner article in this supplement)

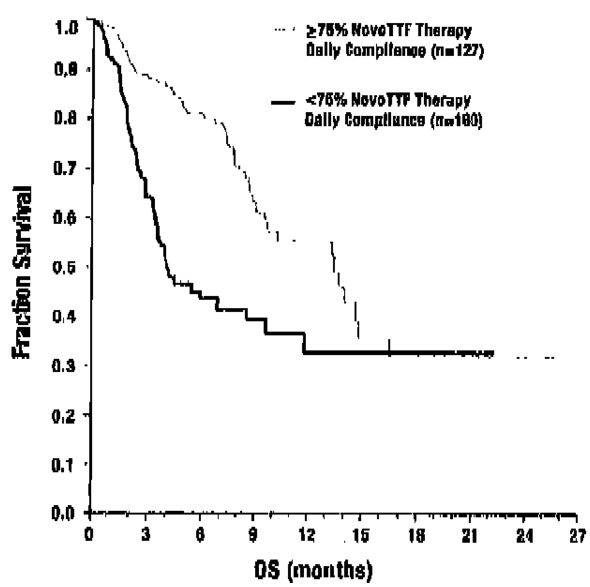

Figure 3.

Table 4. Results of Subgroup Analyses of Overall Survival (OS) in Patients With Recurrent Glioblastoma Multiforme Treated With NovoTTF Therapy in PRiDe Based on Prognostic Factors Significantly Correlated With OS in the Cox Proportional Hazards

Variable	Median OS (mo)	Hazard Ratio	*P* Value
No. of recurrences			
1st	20	—	—
2nd	8.5	0.6 (95% CI, 0.4–0.9)	.0271[a]
3rd-5th	4.9	0.3 (95% CI, 0.2–0.5)	<.0001[b]
Compliance			
≥75%	13.5	0.4 (95% CI, 0.3–0.6)	<.0001
<75%	4.0		
Karnofsky performance status (KPS)			
90–100	14.8	—	—
70–90	7.7	0.6 (95% CI, 0.4–0.9)	.0070[c]
10–60	6.1	0.4 (95% CI, 0.2–0.6)	<.0001[d]
Bevacizumab use			
Naïve	13.4	0.5 (95% CI, 0.4–0.7)	<.0001
Prior use	7.2		
Debulking surgery			
No	8.9	1.1 (95% CI, 0.8–1.5)	.7927
Yes (any surgery)	9.8		

[a] First recurrence compared to 2nd recurrence.
[b] First recurrence compared to 3rd–5th recurrence.
[c] KPS 90–100 compared to KPS 70–80.
[d] KPS 90-100 compared to KPS 10–60.

recently reported similar findings when re-examining data from the EF-11 trial: median OS was significantly longer with a monthly compliance rate for NovoTTF Therapy ≥75% than <75% (7.7 *v* 4.5 months, $P = .042$). The compliance findings from each of these studies are consistent with the mechanism of action of NovoTTF Therapy, which depends on almost continuous administration (≥ 18 hours per day) for a prolonged period of time (≥4 weeks).[21,22] However, patients in PRiDe who had suboptimal compliance were also found to have lower KPS and were, in general, at later stages of their disease. It is unclear whether they also may have had larger tumors or inadequate social support. Nevertheless, consistent with previous findings, our data suggest that applying NovoTTF Therapy to patients with higher performance status, earlier in their recurrence and ensuring treatment compliance, can maximize clinical benefit.

Additional analyses uncovered other prognostic factors that were important for patients in PRiDe. Of interest, in our subgroup analysis, 55.1% of patients in PRiDe who received prior bevacizumab therapy demonstrated a shorter median OS of 7.2 months, as compared to a median OS of 13.4 months in bevacizumab-naïve patients. The shorter survival in patients treated previously with bevacizumab may be a result of acquired tumor resistance and development of a more aggressive phenotype with infiltrative tumor progression on MRI.[9,10] Moreover, patients with recurrent GBM tumors that progress while on bevacizumab therapy are typically resistant or refractory to subsequent cytotoxic chemotherapy,[1,11,12] and have a median OS of just 2.7 months. Therefore, the PRiDe data suggest that at least a percentage of bevacizumab-resistant tumors remain responsive to NovoTTF Therapy. Future analysis of responders and nonresponders to NovoTTF Therapy will need to include molecular genetic analysis of the tumor (and especially MGMT methylation status), the estimated tumor size (volume) as measured by fluid attenuated inversion recovery sequence on MRI, and more detailed analysis of the extent of resection.

Our analysis of KPS in PRiDe also demonstrated that higher KPS correlated with longer OS. It is unclear at this time whether or not patients who had KPS 90–100 had smaller tumors than the rest of the cohort or perhaps more extensive resections. KPS is often, but not always, a measure of tumor size, particularly the microscopic invasive component of the glioblastoma. Whether or not the median tumor size, as measured by gadolinium-enhanced T1-weighted and/or FLAIR MRI, differ between the subgroup with KPS 90–100 versus 70–90 and 10–60 remains to be determined. Of note, age was not a predictor of OS in the PRiDe dataset when evaluated either by direct correlation (Pearson correlation coefficient) or a Cox proportional hazards model ($P = .20$). In addition, age was

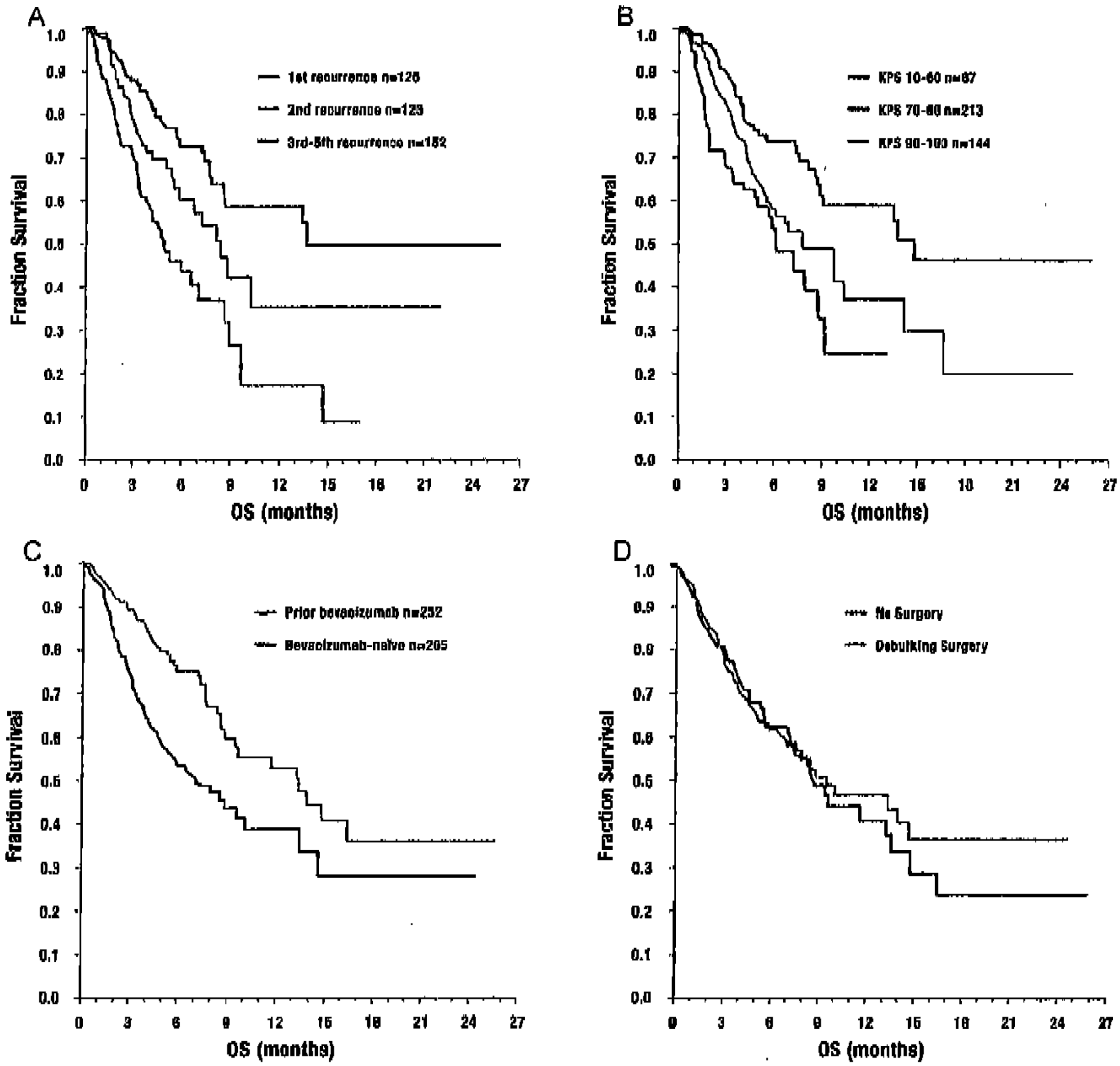

Figure 4. Kaplan-Meier overall survival (OS) curves for recurrent glioblastoma multiforme patients treated with NovoTTF Therapy in PRiDe based on (A) recurrence number, (B) Karnofsky performance status (KPS), (C) prior bevacizumab use, and (D) prior debulking surgery, respectively.

not correlated with compliance in the PRiDe (correlation coefficient = 0.02; $P = .37$). Taken in the context of the overall efficacy results, these findings suggest NovoTTF Therapy works well for patients of all ages and that advanced age is not associated with lower compliance. It would also be interesting to know if marital status (or other measures of patient support) influence compliance and survival, but data on marital status were not collected in PRiDe.

Finally, the PRiDe dataset did not capture patients on combination treatments in which additional biologic therapy or chemotherapy were added to NovoTTF Therapy in a combined regimen. It is possible that the longer survival seen in clinical practice with NovoTTF Therapy compared to NovoTTF monotherapy in the EF-11 trial is a reflection of combination use of NovoTTF Therapy with biological agents or cytotoxic chemotherapy. In fact, preclinical data have suggested that TTFields are additive or even synergistic with chemotherapies in cell culture.[33–35] Therefore, the potential benefits of combining NovoTTF Therapy with other systemic therapies warrant further investigation. A phase III trial of NovoTTF Therapy together with temozolomide compared to temozolomide alone is currently

ongoing in patients with newly diagnosed glioblastoma. The results of this trial will shed light on the possible additive effects of NovoTTF Therapy and systemic chemotherapy.

In summary, PRiDe and the EF-11 trial represent one of the largest datasets of patients with recurrent GBM published to date, containing 700 patients in total, 567 of whom were treated with NovoTTF Therapy. The results, individually and collectively, provide further support for the use of NovoTTF Therapy to treat recurrent, supratentorial GBM. Observations from the post-marketing registry demonstrate that the safety and efficacy observed with NovoTTF Therapy in a clinical trial extend to the real-world, clinical practice setting. Future investigations may need to include NovoTTF Therapy in combination with other recurrent GBM treatments, which together may have additive or synergistic effects on patient outcome.

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Neuro-oncology (G Lesser, Section Editor)

An Evidence-Based Review of Alternating Electric Fields Therapy for Malignant Gliomas

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Opinion statement

Glioblastoma is a deadly disease and even aggressive neurosurgical resection followed by radiation and chemotherapy only extends patient survival to a median of 1.5 years. The challenge in treating this type of tumor stems from the rapid proliferation of the malignant glioma cells, the diffuse infiltrative nature of the disease, multiple activated signal transduction pathways within the tumor, development of resistant clones during treatment, the blood brain barrier that limits the delivery of drugs into the central nervous system, and the sensitivity of the brain to treatment effect. Therefore, new therapies that possess a unique mechanism of action are needed to treat this tumor. Recently, alternating electric fields, also known as tumor treating fields (TTFields), have been developed for the treatment of glioblastoma. TTFields use electromagnetic energy at an intermediate frequency of 200 kHz as a locoregional intervention and act to disrupt tumor cells as they undergo mitosis. In a phase III clinical trial for recurrent glioblastoma, TTFields were shown to have equivalent efficacy when compared to conventional chemotherapies, while lacking the typical side effects associated with chemotherapies. Furthermore, an interim analysis of a recent clinical trial in the upfront setting demonstrated superiority to standard of care cytotoxic chemotherapy, most likely because the subjects' tumors were at an earlier stage of clonal evolution, possessed less tumor-induced immunosuppression, or both. Therefore, it is likely that the efficacy of TTFields can be increased by combining it with other anti-cancer treatment modalities.

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Introduction

Tumor treating fields (TTFields) represent a novel treatment modality for cancer that utilizes alternating electric fields at an intermediate frequency of 200 kHz. At this specific frequency, TTFields have been shown to penetrate into the head from the surface of the scalp. Computational modeling also showed that the fields are distributed inhomogeneously within the supratentorial regions of the brain, and they tend to become intensified near the ventricles [1•]. At the cellular level, the electromagnetic energy perturbs proteins that have large dipole moments. Cells treated with TTFields exhibited a variety of abnormalities indicative of mitotic catastrophe and aberrant mitotic exit, including cells in polyploidy prophase, rosettes, multi-spindled metaphase, single-spindled metaphase, and asymmetric anaphase [2]. Indeed, cells exhibit violent membrane blebbing as they enter anaphase and attempt to divide. This results in aberrant mitotic exit and subsequent cell death [3••]. Some of the proteins that are critical for the proper progression through mitosis have sufficiently high dipole moments to suggest that they may be targets of TTFields, including the mitotic septin complex and the α/β-tubulin monomeric subunit of tubulin. Septins constitute a family of GTP-binding proteins and septin 2, 6, and 7 oligomerize into a heterotrimer with an extremely large dipole moment of 2711 Debyes [4]. Importantly, this septin complex is required for functions that are necessary for the later stages of cell division. Septin 2, 6, and 7 heterotrimers rapidly polymerize and structurally organize within the cytokinetic furrow as cells exit metaphase. Once it is recruited, it then organizes contractile elements within the cytokinetic furrow above the equatorial cleavage plane by binding to F-actin filaments and spatially regulates myosin activation. RNAi-directed depletion of septin subunits of the heterotrimer results in mitotic catastrophe similar to that seen when cells attempt to divide in the presence of TTFields [5]. We have shown that TTFields disrupt the ability of septins to re-localize to the cytokinetic furrow and reduce the accumulation of F-actin [3••]. Therefore, TTFields affect tumor cells by interfering with their ability to complete mitosis by exerting electromagnetic induction forces that interfere with the function of proteins with high dipole moments [2, 3••].

TTFields therapy has been shown to have equivalent efficacy when compared to the best physician's choice chemotherapy in a registration phase III clinical trial for recurrent glioblastoma [6]. This led to the FDA approval on April 8, 2011 for recurrent glioblastoma [Http://Www.Accessdata.Fda.Gov/Cdrh_Docs/Pdf10/P100034a.Pdf]. Interim analysis of the most recent phase III study in the newly diagnosed setting showed a significant improvement of outcomes leading to a crossover of subjects from the control arm to the experimental arm of the trial [7]. Here, we review our current understanding of the mechanisms of TTFields therapy, particularly from the physics and cell biology perspectives, as well as the available clinical data when it is applied to the treatment of glioblastoma.

Electric field distribution within the brain

At a frequency of 200 kHz, the electric fields from the surface of the scalp can permeate into the brain. This is because the penetration of electromagnetic waves through any medium is frequency dependent. Past analyses have shown that the permittivity values were similar among the calvarial bone, gray matter, and white matter, while the conductivity values varied somewhat among these three structures [8].

The electric field intensity was directly measured in a patient receiving TTFields therapy while undergoing surgery for obstructive hydrocephalus from a large pineal meningioma at the Rambam Medical Center in Haifa, Israel. The measured intensity of electric field was validated to within 10 % of the simulated value using finite element method simulation [9].

Using finite element analysis, 3-dimensional mapping of the electric field distribution within the brain revealed inhomogeneous distribution of the fields, with a higher field strength near the ventricular horns that is most likely a result of the high conductivity of the cerebrospinal fluid (Fig. 1).

Cell biology effects of alternating electric fields on dividing tumor cells

TTFields disrupt the mitotic process in dividing tumor cells that results in violent membrane blebbing [3••, 10]. This results in the disordering of chromosomes from the metaphase plate during late metaphase or early anaphase, followed by aberrant mitotic exit in the absence of cytokinesis resulting in multinucleated cells and subsequent apoptosis [3••].

The septin 2, 6, and 7 family members heterotrimerize into a protein complex that possesses an extremely large dipole moment of 2711 Debyes, and it is active in mitosis [4]. This complex serves to regulate contractile function within the cytokinetic furrow, and it is likely to provide tensile strength needed within the submembranous cortical cytoskeleton to restrain the hydrostatic pressures within the cytoplasm during cell division. It has been shown to be a target of alternating electric fields, and the disruption of this protein results in disordered segregation of chromosome and cytoplasmic contents [3••].

Following TTFields-induced aberrant mitotic exit, cells exhibit signs of cellular stress that mark them for immune destruction and facilitate immune activation. Specifically, this type of cellular stress causes increased cell surface expression of the endoplasmic reticulum chaparonin calreticulin and the secretion of HMGB1 that acts as a danger signal when released from cells [11]. The presence of calreticulin on the plasma membrane is also seen in virally infected cells, as well as tumor cells exposed to certain chemotherapy agents [12]. This has been termed "immunogenic cell death" to differentiate it from apoptosis, which is immunosuppressive. Immunogenic cell death leads to tumor destruction.

There is a compelling evidence that TTFields increase the anti-tumor immunogenicity in vivo. When highly metastatic VX-2 tumors were injected into the kidney capsule of rabbits and treated with TTFields for 7 days then allowed to grow for an additional 21 days, the number of pulmonary metastases was significantly reduced when compared to untreated control animals [13]. When the lung metastases were recovered from animals, there was increased infiltration of immune cells in the TTFields-treated metastases as compared with the non-treated ones [14].

Treatment

The management of malignant gliomas should be undertaken in a multimodal fashion, with neurosurgical input, radiation oncology expertise, and chemotherapy administration. Now, with the availability of alternating electric fields therapy as a fourth modality of treatment, neuro-oncologists will need to factor in this therapy within the spectrum of available treatments. For newly diagnosed malignant gliomas, maximal safe neurosurgical resection is still

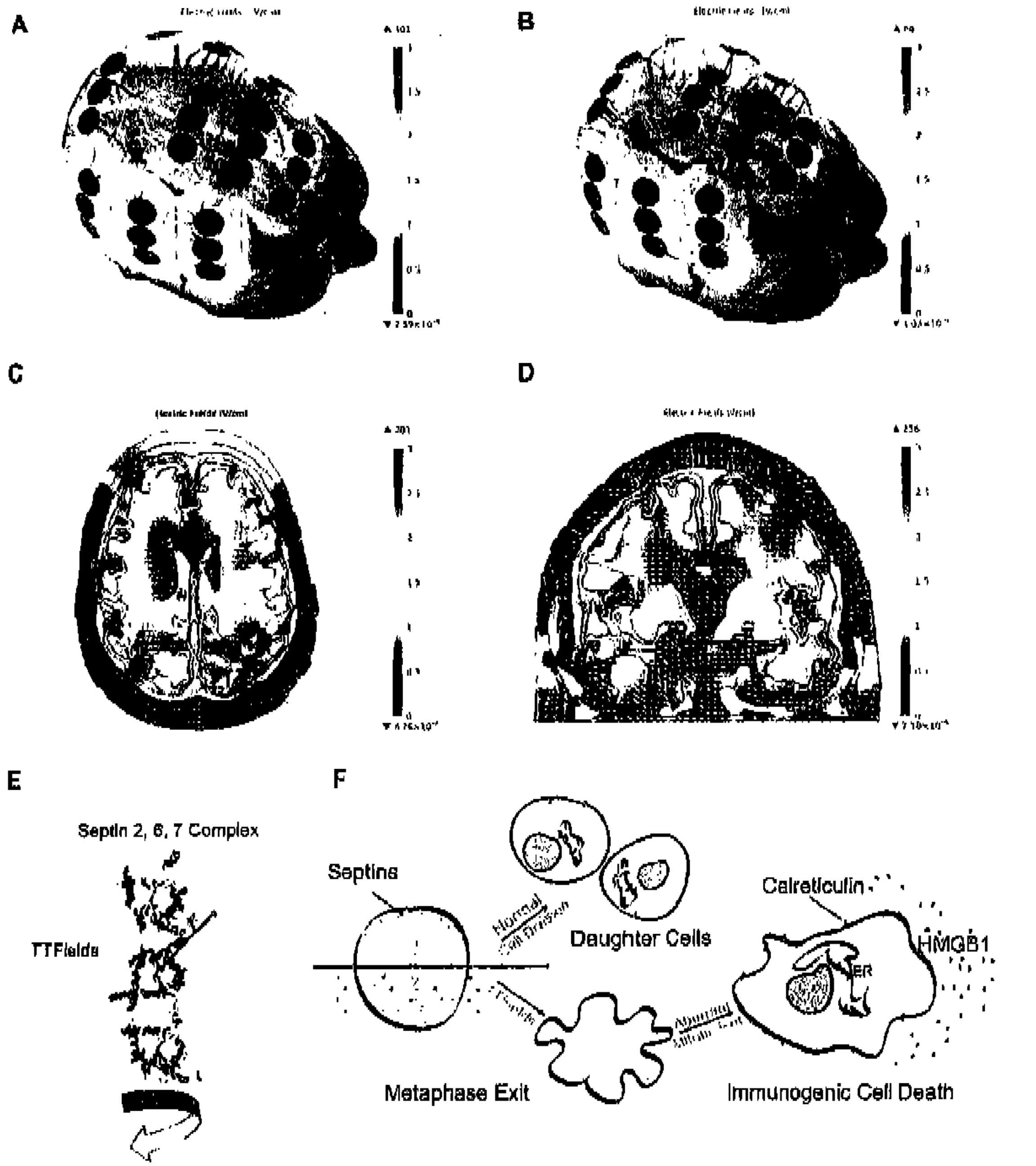

Fig. 1. A 3-dimensional render of a human head with TTFields clinically applied via electrode arrays on a glioblastoma patient whose gross tumor volume is on the right side. **a** Streamlines showing the magnitude of the electric field and direction of the current emanating from each electrode on the surface of the scalp. **b** *Red arrows* indicating vector field of the electric field distribution inside the brain. The intracranial electric fields are displayed in **c** axial and **d** coronal planes. **e** TTFields induce a force on the septin 2, 6, and 7 complex that has an extremely large dipole moment of 2711 Debyes. **f** This results in mitotic catastrophe and aberrant mitotic exit, leading to an increased cell surface expression of the endoplasmic reticulum chaperonin calreticulin and the secretion of HMGB1 that acts as a danger signal when release from cells, both of which are essential for immunogenic cell death.

recommended and resection accomplishes two goals of establishing a histological diagnosis and achieving cytoreduction. Although it has not been subjected to a randomized clinical trial, the best evidence for a benefit of cytoreduction is based on a retrospective analysis showing a 4.2-month survival advantage in patients with at least a 98 % resection versus those with less than 98 % [15]. However, if safe resection is not possible, biopsy to obtain a histological diagnosis is still indicated. Once a diagnosis of glioblastoma is established, patients proceed to standard of care treatment, which consists of external beam, involved-field cranial radiotherapy plus concomitant daily temozolomide, followed by 6 cycles of adjuvant temozolomide [16]. Alternatively, patients may be enrolled in a clinical trial at initial diagnosis and, depending on the conduct of the trial, may either receive treatment independently or in conjunction with standard of care treatment. Although upfront treatment can provide a period of stabilization for the glioblastoma, recurrence is the rule and additional treatments are typically needed to control tumor progression, alleviate neurological deficits, or both.

At the time of tumor recurrence, patients with a Karnofsky performance score of 70 or higher may be eligible for clinical trials. Those who are ineligible can be treated with single-agent bevacizumab or TTFields therapy since both were approved by the FDA for recurrent glioblastoma in 2009 and 2011, respectively. The benefit of bevacizumab was based on two single-arm phase II studies demonstrating a radiographic response rate of 30–40 % [17, 18]. However, infiltrative glioblastoma is the typical pattern of relapse and salvage chemotherapy after bevacizumab failure only offered a median overall survival of 5.2 months and progression-free survival of 2.0 months [19]. Therefore, alternative treatments are desperately needed for this population and TTFields therapy was demonstrated to have equivalent efficacy when compared to chemotherapy in this setting [6]. However, the optimal use of this device and its combination with conventional treatments are awaiting further investigation. Here, we review the currently available clinical data when it is applied to the treatment of glioblastoma, which is also summarized in Table 1.

TTFields therapy for recurrent glioblastoma

At present, the only indication approved by the FDA is for the treatment of recurrent glioblastoma. This is based on the registration phase III clinical trial (ClinicalTrials.gov: NCT00379470) demonstrating equivalent efficacy between TTFields therapy and best physician's choice chemotherapy (based on the best available treatment as offered by the treating physician) [6].

The primary endpoint of the trial was overall survival, and the median overall survival was 6.6 months for TTFields (n=120) versus 6.0 months for the best physician's choice chemotherapy (n=117), with a hazard ratio of 0.86 (95 % CI 0.66–1.12; P=0.27). It is notable that 31 % of the BPC cohort received bevacizumab alone or in combination with chemotherapy. The median progression-free survival of TTFields and the best physician's choice chemotherapy was 2.2 and 2.1 months, respectively, with a hazard ratio of 0.81 (95 % CI 0.60–1.09; P=0.16), and the progression-free survival at 6 months was 21.4 % (95 % CI 13.5–29.3) and 15.1 % (95 % CI 7.8–22.3), respectively (P=0.13). One year survival rate was 20 % in both cohorts.

Table 1. Summary of clinical data on TTFields treatment for malignant gliomas

Phase III trial for newly diagnosed glioblastoma interim analysis	TTFields treatment + temozolomide	Temozolomide alone	Hazard ratio	*P*
Overall survival, median[a]	19.6 months	16.6 months	0.75	0.03
Progression-free survival[a]	7.1 months	4.0 months	0.63	<0.01
Phase III recurrent glioblastoma	TTFields treatment (n=120)	Active chemotherapy (n=117)		
Overall survival, median[b]	6.6 months	6.0 months	0.86 (95 % CI 0.66–1.12)	0.27
1-year survival	20 %	20 %		
2-year survival	8 %	4		
3-year survival	5 %	1 %		
Prognostic factors, median overall survival[c]				
Prior bevacizumab failure	6.0 months (n=23)	3.3 months (n=21)	0.43 (95 % CI 0.22–0.85)	0.02
Prior low-grade glioma	25.3 months (n=12)	7.7 months (n=9)	0.31 (95 % CI 0.09–0.99)	0.05
Tumor size ≥18 cm²	5.6 months (n=39)	3.3 months (n=41)	0.53 (95 % CI 0.32–0.85)	<0.01
Karnofsky performance status ≥80	7.9 months (n=83)	6.1 months (n=77)	0.71 (95 % CI 0.51–0.99)	0.05
TTFields treatment versus bevacizumab	6.6 months (n=120)	4.9 months (n=36)	0.64 (95 % CI 0.41–0.99)	0.05
Progression-free survival, median[b]	2.2 months	2.1 months	0.81 (95 % CI 0.60–1.09)	0.13
PFS at 6 months	21 %	15 %		
Responders[d]	14	7		
Response status, median overall survival				
Partial and complete response versus	24.7 months (n=14)			
Stable disease	7.6 months (n=34)		0.28 (95 % CI 0.14–0.58)	<0.01
Progressive disease	5.5 months (n=59)		0.24 (95 % CI 0.14–0.42)	<0.01
Prognostic factor in TTFields treatment responders[e]				
Overall survival, median				
With prior low-grade glioma	27.7 months			
Without prior low-grade glioma	16.6 months			0.05
Daily dexamethasone dose, median				
Responders	1.0 mg			
Nonresponders	5.2 mg			<0.01
Cumulative dexamethasone dose, median				
Responders	7.1 mg			
Nonresponders	261.7 mg			<0.01
Treatment-related adverse events, ≥grade 2[b,f]				
Hematological	3 %	17 %		
Gastrointestinal	4 %	17 %		
Dermatological	2 %	0 %		
Nervous system disorders	30 %	28 %		
Recurrent glioblastoma from patient registry data set (PRiDe)	PRiDe TTFields treatment (n=457)	EF-11 TTFields treatment (n=120)		
Survival[g]				
1-year survival	44 %	20 %		
2-year survival	30 %	9 %		

Table 1. (Continued)

Phase III trial for newly diagnosed glioblastoma interim analysis	TTFields treatment + temozolomide	Temozolomide alone	Hazard ratio	P
Prognostic factors, median overall survival[g]				
Number of prior recurrences				
First recurrence versus	20 months			
Second recurrence	8.5 months, HR=0.6 (95 % CI 0.4–0.9), P=0.03			
Third to fifth recurrence	4.9 months, HR=0.3 (95 % CI 0.2–0.5), P<0.01			
Compliance				
<75 % versus	4.0 months			
≥75 %	13.5 months, HR=0.4 (95 % CI 0.3–0.6), P<0.01			
Karnofsky performance status				
90–100 versus	14.8 months			
70–90	7.7 months, HR=0.6 (95 % CI 0.4–0.9), P<0.01			
10–60	6.1 months, HR=0.4 (95 % CI 0.2–0.6), P<0.01			
Prior bevacizumab use				
No versus	13.4 months			
Yes	7.2 months, HR=0.5 (95 % CI 0.4–0.7), P<0.01			
Prior debulking surgery				
No versus	8.9 months			
Yes	9.8 months, HR=1.1 (95 % CI 0.8–1.5), P=0.79			

[a]Stupp R, Wong E, Scott C, et al. Neuro-Oncol 2014;16(Suppl 5):v167
[b]Stupp R, Wong ET, Kanner AA, et al. Eur J Cancer 2012;48:2192-2202
[c]Kanner AA, Wong ET, Villano JL, et al. Semin Oncol 2014;41(Suppl 6):S25-S34
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The most common toxicity associated with the device was grade 1 or 2 scalp irritation at a rate of 16 %, but none had severity of grade 3 or 4. The scalp irritation can be managed by applying topical corticosteroid and by shifting of the arrays slightly during each array exchange [20]. The most important advantage associated with the TTFields therapy device, when compared to chemotherapy, is that it has far fewer grade 2 or greater hematological toxicities, 3 versus 17 %, respectively, and fewer adverse gastrointestinal events, 4 versus 17 %, respectively.

Analysis of quality of life demonstrated that patient treated with the device had better cognitive and emotional functions than those treated with chemotherapy while appetite loss, constipation, diarrhea, fatigue, nausea, vomiting, and pain were more often seen in patients treated with chemotherapy. Based on the equivalent efficacy results and the lack of serious toxicities, the TTFields therapy device was approved by US FDA on April 8, 2011 for the treatment of recurrent glioblastoma.

Post hoc analysis showed that a higher proportion of responders had secondary glioblastoma than nonresponders [21••]. Five of the 14 responders (36 %) treated with TTFields monotherapy had prior low-grade histology while none of the seven responders (0 %) treated with the best physician's choice chemotherapy did.

The analysis also showed that responders used less dexamethasone than nonresponders [21••]. In the TTFields therapy cohort, the median daily dexamethasone dose used was 1.0 mg for responders versus 5.2 mg for nonresponders ($P=0.0019$) and the median cumulative dexamethasone dose was 7.1 mg for responders versus 261.7 mg for nonresponders ($P<0.0001$). In the best physician's choice chemotherapy cohort, the median daily dexamethasone dose used was 1.2 mg for responders versus 6.0 mg for nonresponders ($P=0.0041$) and the median cumulative dexamethasone dose was 348.5 mg for responders versus 242.3 mg for nonresponders ($P=0.9520$). These data suggest that concurrent dexamethasone use may influence the efficacy of TTFields therapy.

TTFields therapy as used in clinical practice

Patients who received treatment from the TTFields device in clinical practice may have different clinical characteristics and outcomes from those who participated in the registration trial. To determine whether or not this is the case, a patient registry dataset (PRiDe) was developed in an effort to capture clinical practice data pertaining to the use of TTFields therapy. At the time of publication, this dataset included 457 patients from 91 treatment centers in the USA [22•].

The median OS was 9.6 months among patients treated in PRiDe as compared to 6.6 months in the TTFields monotherapy arm in the phase III trial while the 1-year OS rate was also longer at 44 % as compared to 20 %, respectively [6, 22•]. It is important to note that some patients in PRiDe may have used other treatments, such as conventional cytotoxic chemotherapy, bevacizumab, or even alternative medicine, in conjunction with TTFields therapy, but this aspect of treatment was not adequately captured because this dataset is from a registry.

About 33 % of patients at their first glioblastoma recurrence used TTFields therapy as compared to only 9 % in the registration phase III clinical trial [22•].

Favorable prognostic factors for patient survival include treatment with TTFields therapy at first or second relapses versus third or later recurrences, as well as no prior bevacizumab use [22•].

TTFields therapy for newly diagnosed glioblastoma

TTFields therapy is currently being tested in a randomized phase III clinical trial for subjects with newly diagnosed glioblastoma (NCT0916409). The goal of this study is to compare the efficacy of TTFields plus adjuvant temozolomide versus adjuvant temozolomide alone by randomizing the subjects to the respective treatment arms in a 2:1 fashion, after the completion of initial treatment with radiation and concomitant daily temozolomide [16]. The primary endpoint is progression-free survival, and the secondary endpoints are overall survival, progression-free survival at 6 months, survival at 1 and 2 years, as well as quality of life assessment. So far, all 700 pre-specified subjects have been enrolled and randomized.

In a pre-specified interim analysis of the first 315 subjects after a minimum follow-up of 18 months, the intent-to-treat cohort received TTFields plus temozolomide (n=210) had a longer progression-free survival than the cohort treated with temozolomide alone (n=105), median 7.1 (95 % CI 5.9–8.2) months versus 4.0 (95 % CI 3.0–4.3) months (HR=0.63, Log rank P= 0.0014). The median overall survival also favors the TTFields plus temozolomide group, 19.6 (95 % CI 16.5–24.1) months versus 16.6 (95 % CI 13.5–19.1) months, respectively (HR=0.75, Log rank P=0.034), as well as the per protocol population that started the second cycle of treatment, 20.5 (95 % CI 16.5–24.1) months (n=196) versus 15.5 (95 % CI 13.5–19.1) months (n=84), respectively (HR=0.67, Log rank P=0.0042).

There were no unexpected adverse events between the TTFields plus temozolomide and the temozolomide alone cohorts, and respective grade 3 and 4 hematological toxicities (12 versus 9 %), gastrointestinal disorders (5 versus 2 %), and convulsions (7 versus 7 %) were similar. Scalp reaction, however, was more common in the device-treated cohort, 49 % for grades 1 and 2 as well as 7 % for grade 3 and 4 toxicities, than the temozolomide-only cohort, 5 % for grade 1 and 2 toxicities as well as 5 % for grade 3 and 4 toxicities.

The follow-up of the remaining trial subjects will most likely mature in another year such that final data from the trial will be available by the end of 2016.

Additional investigational studies of TTFields therapy for the central nervous system or other malignancies

Combinations with TTFields are being studied in patients with recurrent glioblastoma including bevacizumab (NCT01894061) and bevacizumab together with hypofractionated stereotactic irradiation (NCT01925573).

TTFields therapy is currently being investigated in patients with other types of central nervous system malignancies, including its use for recurrent atypical and anaplastic meningiomas (NCT01892397), as well as in those patients with 1–5 brain metastases from non-small cell lung cancer (NCT01755624).

TTFields therapy is also being investigated in systemic malignancies, including its use in combination with gemcitabine for advanced pancreatic adenocarcinoma (NCT01971281), in combination with paclitaxel in recurrent ovarian carcinoma (NCT02244502), as well as in combination with pemetrexed and cisplatin or carboplatin for malignant pleural mesothelioma (NCT02397928).

Compliance with Ethics Guidelines

Conflict of Interest

Eric T Wong received an unrestricted grant from Novocure for the investigation of the cell biology effects of TTFields; participated in the registration trial for recurrent glioblastoma and the PRiDe dataset; and has received sponsored clinical research through grants from AngioChem, AstraZeneca, Cephalon, Eli Lilly, Northwest Biotherapeutics, Novartis, Pfizer, and Plexxikon.

Edwin Lok declares that he has no conflict of interest.

Kenneth D. Swanson received an unrestricted grant from Novocure for the investigation of the cell biology effects of TTFields and has also received a reimbursement for travel expenses for training on use of laboratory equipment and an honorarium for a lecture at Novocure headquarters to present the results of basic research studies.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Open Access

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The post hoc analysis demonstrated the importance of the dose of concurrent dexamethasone used by subjects in the phase III trial that had an association with response to TTFields therapy.

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This paper documented the pattern of TTFields therapy usage in clinical practice.

FULL PAPER

BJC

Keywords: dexamethasone; glioblastoma; NovoTTF-100A; tumour immunology; chemotherapy

Dexamethasone exerts profound immunologic interference on treatment efficacy for recurrent glioblastoma

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Background: Patients with recurrent glioblastoma have a poor outcome. Data from the phase III registration trial comparing tumour-treating alternating electric fields (TTFields) *vs* chemotherapy provided a unique opportunity to study dexamethasone effects on patient outcome unencumbered by the confounding immune and myeloablative side effects of chemotherapy.

Methods: Using an unsupervised binary partitioning algorithm, we segregated both cohorts of the trial based on the dexamethasone dose that yielded the greatest statistical difference in overall survival (OS). The results were validated in a separate cohort treated in a single institution with TTFields and their T lymphocytes were correlated with OS.

Results: Patients who used dexamethasone doses >4.1 mg per day had a significant reduction in OS when compared with those who used ⩽4.1 mg per day, 4.8 *vs* 11.0 months respectively ($\chi^2 = 34.6$, $P < 0.0001$) in the TTField-treated cohort and 6.0 *vs* 8.9 months respectively ($\chi^2 = 10.0$, $P < 0.0015$) in the chemotherapy-treated cohort. In a single institution validation cohort treated with TTFields, the median OS of patients who used dexamethasone >4.1 mg per day was 3.2 months compared with those who used ⩽4.1 mg per day was 8.7 months ($\chi^2 = 11.1$, $P = 0.0009$). There was a significant correlation between OS and T-lymphocyte counts.

Conclusions: Dexamethasone exerted profound effects on both TTFields and chemotherapy efficacy resulting in lower patient OS. Therefore, global immunosuppression by dexamethasone likely interferes with immune functions that are necessary for the treatment of glioblastoma.

Patients with recurrent glioblastoma have limited treatment options. Bevacizumab is a standard of care for patients with recurrent glioblastoma and it produces an objective response rate of 25–60% (Wong *et al*, 2011). However, its ability to prolong patient overall survival (OS) is questionable (Iwamoto and Fine, 2010; Reardon *et al*, 2012). The NovoTTF-100A device is another FDA-approved treatment for recurrent glioblastoma that works by emitting tumour-treating alternating electric fields (TTFields) via two pairs of transducer arrays placed orthogonally on the scalp and acts to perturb tumour cells during mitosis (Kirson *et al*, 2004, 2007; Gera *et al*, 2015). Preclinical data show that cells affected by TTFields exhibit violent plasma membrane blebbing that disrupts the normal spatial ordering of the mitotic chromosomes. This results in asymmetric chromosome segregation and aneuploidy owing to defects in cytokinesis and aberrant mitotic exit. Furthermore, these cells also exhibit signs of stress that include elevated cell surface expression of calreticulin, which makes them more readily detectable by phagocytic immune cells, facilitating an immune response against the tumour (Lee *et al*, 2013). Importantly, the NovoTTF-100A device was demonstrated to possess equivalent efficacy when compared with best physician's choice (BPC) chemotherapy in the registration phase III clinical trial, but without the myeloablative toxicities associated with systemic chemotherapies that may cause secondary systemic infection or interference with immune effector function (Vecht *et al*, 1994; Hughes *et al*, 2005; Stupp *et al*, 2012; Fonkem and Wong, 2012).

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More recently, a prespecified interim analysis of the results from an upfront phase III clinical trial in newly diagnosed glioblastoma patients, comparing NovoTTF-100A plus adjuvant temozolomide *vs* adjuvant temozolomide alone, revealed significantly improved patient outcome with a respective progression-free survival of 7.1 *vs* 4.0 months and OS of 19.6 *vs* 16.6 months (Stupp *et al*, 2014). Compared with newly diagnosed glioblastomas, patients with recurrent glioblastoma likely have several factors that led to a worse outcome, including clonal evolution of the tumour, evasion of the immune system and reduction of immune competence because of prior exposure to chemotherapy.

Dexamethasone is commonly used to treat neurologic symptoms caused by the glioblastoma (Vecht *et al*, 1994). However, it also has a plethora of systemic toxicities, including gastrointestinal haemorrhage with or without perforation, infection, and hyperglycaemia (Heimdal *et al*, 1992). Although dexamethasone has not been shown to interfere directly with the efficacy of treatments against glioblastoma, there is emerging evidence from both preclinical and clinical data in other malignancies to suggest that dexamethasone may affect the patient's antitumour immunity. First, although the immune system has evolved multiple mechanisms to recognise and eliminate neoplastic cells (Senovilla *et al*, 2013), tumours emerge within the patient when they escape immune surveillance (Mittal *et al*, 2014). At this point, the tumour further subverts the immune system by eliciting normal wound healing and tissue remodelling responses, whereas promoting a state of immune privilege within the tumour microenvironment (Schreiber *et al*, 2011). In this setting, dexamethasone may potentiate existing local immunosuppression via global induction of IκBα and inhibition of NF-κB activity in lymphocytes, resulting in global immunosuppression (Auphan *et al*, 1995). Second, dexamethasone can lower the number of CD4$^+$ lymphocytes in newly diagnosed patients with glioblastoma treated with radiation alone or in combination with temozolomide, and this attentuated CD4$^+$ lymphocyte count is associated with increased infections and decreased survival (Hughes *et al*, 2005; Grossman *et al*, 2011). Lastly, recent clinical trial data have shown that there were more systemic and central nervous system responders to ipilimumab, an immune checkpoint inhibitor, in the cohort taking no dexamethasone as compared with the cohort taking dexamethasone, suggesting that dexamethasone interferes with the efficacy of ipilimumab (Margolin *et al*, 2012).

In this paper, we present evidence that immune suppression by dexamethasone markedly interferes with the clinical efficacy of two disparate therapies for recurrent glioblastoma: electric field-based therapy delivered by the NovoTTF-100A as well as conventional chemotherapies. Unlike prior clinical trials, the cohort treated with TTField monotherapy offered us an opportunity to study unambiguously the effect of dexamethasone on patient survival unencumbered by concurrent chemotherapies that suppress the immune system. We also present data that strongly support a role for immune competence in effecting TTField treatment by analysing T-cell subsets measured in a separate cohort of patients for validation.

PATIENTS AND METHODS

Patients. Subjects signed informed consent from their respective treating institutions before participation in the phase III trial comparing NovoTTF-100A *vs* BPC chemotherapy (Fonkem and Wong, 2012; Stupp *et al*, 2012). A *post hoc* analysis of the dexamethasone effect on the two cohorts was performed based on anonymised data obtained from the sponsor, from whom the corresponding author had full access to the primary data. The outcome of the analysis was then validated retrospectively, under an institutional review board-approved protocol from Dana Farber/Harvard Cancer Center (protocol no. 12-519), using a separate cohort of patients who were treated with NovoTTF-100A and bevacizumab at Beth Israel Deaconess Medical Center.

Statistical analysis. Statistical analyses were performed by using R statistics base package (http: //www.r-project.org) and its libraries. Two-tailed Wilcoxon's rank-sum test with continuity correction was used to determine whether two independent groups of data were statistically different from each other. A modified binary search algorithm (Knuth, 1971; Tøndel *et al*, 2002), written in R, was used to iteratively partition data in both two and three dimensions. The Loess local nonparametric polynomial regression was used to perform curve fitting of the OS as a function of dexamethasone dose (Cleveland, 1979; Shipley and Hunt, 1996; Cleveland and Loader, 1996) and OS was analyzed using Kaplan–Meier statistics (Kaplan and Meier, 1958).

RESULTS

Effect of dexamethasone on TTField therapy and BPC chemotherapy. Our previous *post hoc* analysis of responders in the phase III trial demonstrated that responders to TTField therapy required significantly lower doses of dexamethasone compared with non-responders (Wong *et al*, 2014). We therefore investigated further whether there was a threshold dose of dexamethasone that affected outcome within the entire trial population. Using an unsupervised binary partitioning algorithm (Knuth, 1971; Tøndel *et al*, 2002), we stratified the TTField therapy cohort based on the dexamethasone dose that yielded the greatest statistical difference in median OS. The results revealed that subjects who used >4.1 mg per day dexamethasone ($n = 64$) exhibited a significantly shortened median OS of 4.8 months (95% confidence interval (CI): 3.9–6.0) *vs* those who used ⩽4.1 mg per day ($n = 56$), with a median OS of 11.0 months (95% CI: 8.8–16.6) ($\chi^2 = 34.6$, $P < 0.0001$; Figure 1A). We then used the same dexamethasone cutoff to stratify control patients in the BPC chemotherapy cohort and observed a similar, albeit less robust, dichotomisation, with a respective median OS of 6.0 months (95% CI: 3.5–8.3) ($n = 54$) *vs* 8.9 months (95% CI: 7.2–16.1) ($n = 63$) ($\chi^2 = 10.0$, $P = 0.0015$; Figure 1B) for those receiving >4.1 *vs* ⩽4.1 mg per day of dexamethasone, respectively. There are two potential explanations for these results: either patients with larger, more aggressive tumours required a higher dose of dexamethasone for symptom control or doses of dexamethasone >4.1 mg per day interfered with both therapeutic interventions used in this trial. However, tumour size did not differ statistically between patient cohorts that used dexamethasone at either >4.1 or ⩽4.1 mg per day (Figures 1C and D). Therefore, factors other than tumour size influence the OS of subjects receiving high *vs* low doses of dexamethasone.

To further investigate the effect of dexamethasone on patient outcome, we compared the survival characteristics of the cohort treated with TTField therapy to the one treated with BPC chemotherapy in the respective dexamethasone dosage groups. First, we compared the two treatment groups when the dosage of dexamethasone used was ⩽4.1 mg per day. Although the two OS curves overlapped ($\chi^2 = 0.9$, $P = 0.3510$; Figure 2A), we detected a marked separation between these two curves at time points less than the median OS. Indeed, when we compared the survival curves of the two cohorts for subjects who used dexamethasone ⩽4.1 mg per day and possessed survival times of less than the median OS, we found a significant difference between the two subgroups, with a median OS of 6.6 (range 1.4–10.1) months for the TTField-treated subgroup ($n = 31$) *vs* 3.9 (range 0.0–8.6) months for the BPC chemotherapy-treated subgroup ($n = 40$) ($P = 0.0015$; Figure 2C). However, for subjects who lived longer

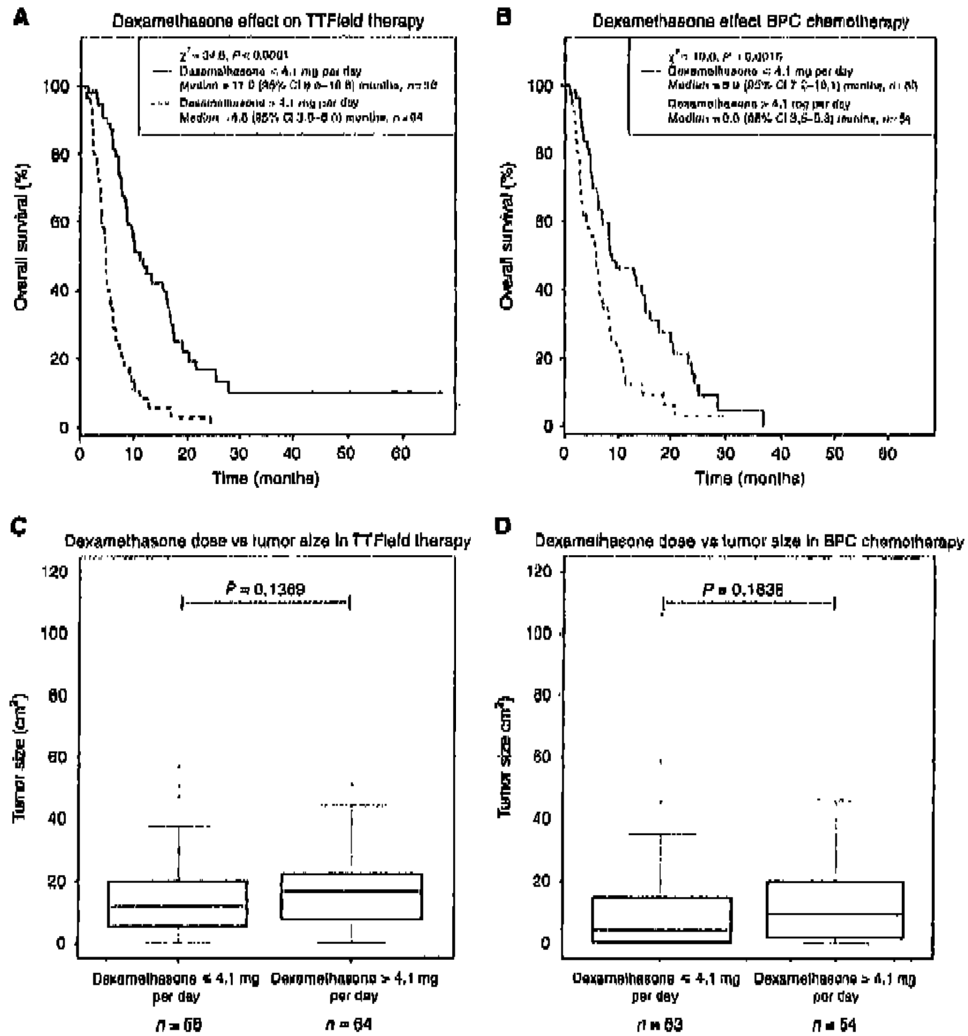
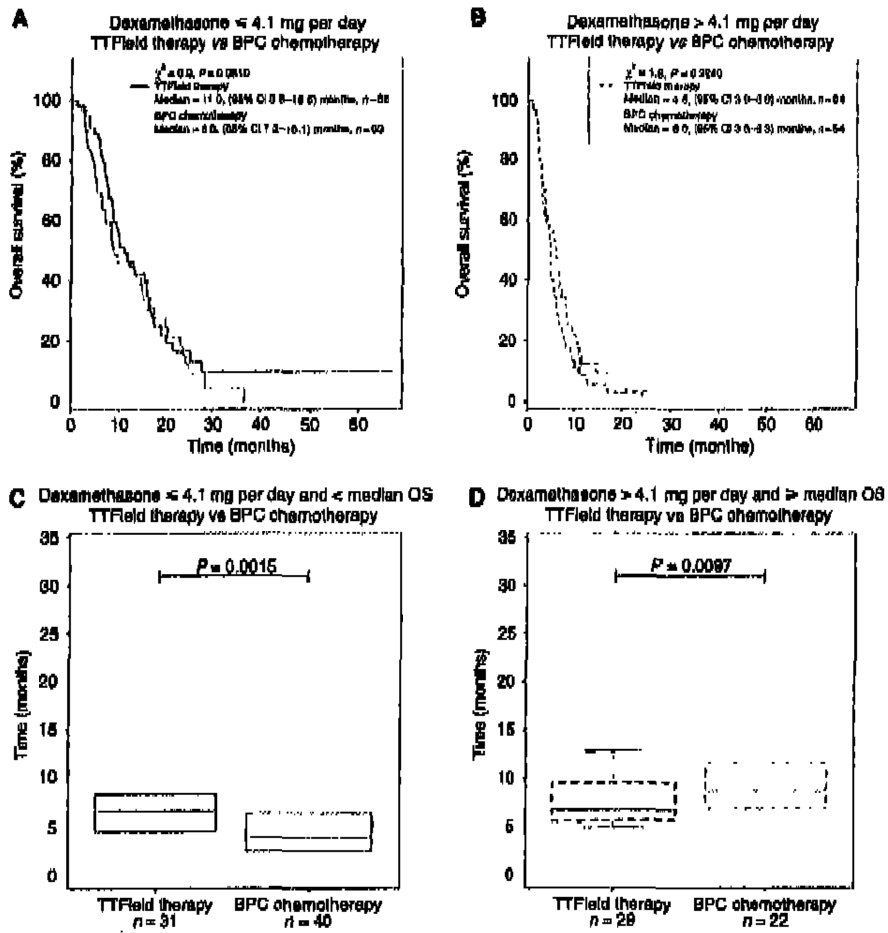


Figure 1. Kaplan–Meier OS and tumour size with respect to dexamethasone requirement of ≤4.1 *vs* >4.1 mg per day from subjects enrolled in the phase III trial comparing TTField therapy vs BPC chemotherapy. (**A**) Subjects enrolled in the TTField treatment arm taking dexamethasone ≤4.1 (solid blue) *vs* >4.1 (dashed blue) mg per day, which was determined by an unsupervised binary partitioning algorithm. Subjects who used ≤4.1 mg per day of dexamethasone ($n = 56$) had a median OS of 11.0 months (95% CI: 8.8–16.6) as compared with those who used >4.1 mg per day ($n = 64$) had a median OS of 4.8 months (95% CI: 3.9–6.0) ($\chi^2 = 34.6$, $P < 0.0001$). (**B**) Subjects enrolled in the BPC chemotherapy arm taking dexamethasone ≤4.1 (solid red) *vs* >4.1 (dashed red) mg per day was determined by the same unsupervised binary partitioning algorithm. Subjects who used ≤4.1 mg per day of dexamethasone ($n = 63$) had a median OS of 8.9 months (95% CI: 7.2–16.1) as compared with those who used >4.1 mg per day ($n = 54$) had a median OS of 6.0 months (95% CI: 3.5–8.3) ($\chi^2 = 10.0$, $P = 0.0015$). (**C**) Box-and-whisker plot of bidimensional tumour size in the TTField therapy cohort that received dexamethasone ≤4.1 vs >4.1 mg per day. Subjects who took dexamethasone ≤4.1 mg per day ($n = 56$) had a median tumour size of 11.9 (range 0.0–56.7) cm² as compared with those who used >4.1 mg per day ($n = 64$) had a median tumour size of 16.8 (range 0.3–51.0) cm² ($P = 0.1369$). (**D**) Box-and-whisker plot of bidimensional tumour size in the BPC chemotherapy cohort that received dexamethasone ≤4.1 *vs* >4.1 mg per day. Subjects who took dexamethasone ≤4.1 mg per day ($n = 63$) had a median tumour size of 4.2 (range 0.0–11.2) cm² as compared with those who used >4.1 mg per day ($n = 54$) had a median tumour size of 9.6 (range 0.0–46.0) cm² ($P = 0.1638$).

than the median OS, there was no difference in the OS curves, with a median OS of 16.7 (range 11.0–66.9) months for the TTField-treated subgroup ($n = 25$) *vs* 16.8 (range 8.9–36.7) months for the BPC chemotherapy-treated subgroup ($n = 23$) ($P = 0.5773$; Figure 2E). In contrast, among subjects who received high dexamethasone doses of >4.1 mg per day, the overlapping OS curves ($\chi^2 = 1.5$, $P = 0.2240$; Figure 2B) appeared to diverge for the subjects whose survival were greater than the median OS. Remarkably, the TTField-treated subgroup was worse compared with the BPC chemotherapy-treated subgroup when treated with dexamethasone doses >4.1 mg per day, with a respective median OS of 6.7 (range 4.8–24.3) months ($n = 29$) *vs* 8.7 (range 6.0–29.6) months ($n = 22$) ($P = 0.0097$; Figure 2D). However, for subjects whose survival were less than the median OS and used >4.1 mg per day dexamethasone, there was no difference between the TTField-treated and the BPC chemotherapy-treated subgroups, with the former having a median OS of 3.0 (range 0.6–4.5) months ($n = 35$) as compared with the latter having a median OS of 2.8 (range 0.2–5.8) months ($n = 32$) ($P = 0.8456$; Figure 2E). Collectively, the data in Figures 2C and D indicate that the extent



E

	Dex ≤4.1 mg per day Median OS (range)		Dex >4.1 mg per day Median OS (range)	
	TTField therapy	BPC Chemotherapy	TTField therapy	BPC chemotherapy
<Median OS in A & B	6.6 (1.4–10.1) months	3.9 (0.0–8.6) months	3.0 (0.6–4.6) months	2.6 (0.3–5.6) months
	P=0.0015		P=0.6456	
≥Median OS in A & B	16.7 (11.0–60.9) months	16.9 (8.9–36.7) months	6.7 (4.8–24.3) months	8.7 (6.0–29.6) months
	P=0.6773		P=0.0097	

Figure 2. Comparison of OS in subjects treated with TTField therapy *vs* BPC chemotherapy segregated by dexamethasone usage. (A) Comparison of subjects using dexamethasone ≤4.1 mg per day in both TTField therapy (blue) and BPC chemotherapy (red) arms. (B) Comparison of subjects using dexamethasone >4.1 mg per day in both TTField therapy and BPC chemotherapy arms. (C) Box-and-whisker plot of OS between TTField *vs* BPC chemotherapy-treated subjects using ≤4.1 mg per day of dexamethasone and <the median OS in (A). The median OS was 6.6 months (range 1.4–10.1) for TTField-treated subjects ($n = 31$) *vs* 3.9 months (range 0.0–8.6) for BPC chemotherapy-treated subjects ($n = 40$) ($P = 0.0015$). (D) Box-and-whisker plot of OS between TTFields *vs* BPC chemotherapy-treated subjects using >4.1 mg per day of dexamethasone and ≥the median OS in (B). The median OS was 6.7 months (range 4.8–24.3) for TTField-treated subjects ($n = 29$) *vs* 8.7 months (range 6.0–29.6) for BPC chemotherapy-treated subjects ($n = 22$) ($P = 0.0097$). (E) Median OS, range, and *P*-values for the four subgroups: (i) dexamethasone ≤4.1 mg per day and <median OS in (A), (ii) dexamethasone >4.1 mg per day and <median OS in (B), (iii) dexamethasone ≤4.1 mg per day and ≥median OS in (A), and (iv) dexamethasone >4.1 mg per day and ≥median OS in (B).

of dexamethasone exposure not only predicted treatment efficacy but also strongly suggest that TTField therapy is superior to BPC chemotherapy in the setting of low dexamethasone usage. However, under the influence of higher dexamethasone usage, the benefit of TTField therapy appeared to be negated to a greater extent when compared with BPC chemotherapy as if TTField-treated subjects were not provided with any therapy at all.

Dose-dependent effect of dexamethasone on treatment efficacy. We next asked whether or not dexamethasone has a dose-dependent influence on treatment efficacy by analysing the entire dose spectrum used in the trial. We partitioned the TTField-treated cohort using a dexamethasone dose cutoff from 0.0 to 37.0 mg per day, plotted the respective median OS of the groups at ⩽cutoff or >cutoff *vs* successive dexamethasone dosages, and fitted the data with the best curves using the nonparametric Loess local polynomial regression (Figure 3) (Cleveland, 1979; Cleveland and Loader, 1996; Shipley and Hunt, 1996). In addition, we plotted the log-rank *P*-values of the dichotomised groups in each successive dexamethasone dosage and found two nadir *P*-values of 0.00000008 and 0.00002524 corresponding to dexamethasone doses of 4.1 and 7.8 mg per day, respectively. We observed that there was decremental OS starting at a dexamethasone dose of 4.1 mg per day and, with successive increases of dexamethasone, reached an inflection point at 7.8 mg per day, after which the rate of OS decreased slowly (Figure 3A).

We also performed the same dose-dependent analysis of dexamethasone in the BPC chemotherapy-treated cohort and found a nadir *P*-value of 0.00163291 at 3.3 mg per day and another of 0.00011858 at 7.5 mg per day. Similarly, the best-fit curve derived in Figure 3B also suggests that the dexamethasone dose near 4 mg per day may also represent a point at which decremental OS can be observed with successive increases in dexamethasone dosage. This progressive decrement in OS occurred with successive increases of dexamethasone until an inflection point is observed at a dose near 7.5 mg per day, after which the rate of OS decreased slowly. Taken together, both cohorts experienced interference from dexamethasone at a dose near 4.0 mg per day and a maximal effect was observed near 7.5 mg per day.

Validation of the dexamethasone effect on TTField-treated patients from a single institution. We next proceeded to validate the observed dexamethasone effect on patient outcome within the trial by retrospectively analysing our own single-institution cohort. From November 2012 to February 2014, we treated 38 patients (Table 1) using TTField monotherapy as treatment or in combination with bevacizumab, whereas dexamethasone usage was aggressively reduced. Three patients who were referred specifically to our institution did not receive TTField therapy because of patient choice of other treatments, severe medical comorbidities, or advanced intracranial disease that was deemed more suitable for hospice care. Among the remaining 35 patients, their median OS was 4.3 months (95% CI: 3.5–8.7). To properly compare this cohort with the subjects enrolled in the phase III trial, we included only those with a KPS ⩾70 or greater ($n=23$) in our validation set. This sub-population exhibited a median OS of 8.0 months (95% CI: 3.8–13.8) compared with 3.2 months (95% CI: 1.4–NA) for the remaining patients with a KPS <70 ($n=12$) ($\chi^2=8.5$, $P=0.0035$; Figure 4A). We then applied a cutoff of dexamethasone 4.1 mg per day as was found in our previous binary partitioning analysis. Patients who used dexamethasone ⩽4.1 mg per day had a significantly longer OS compared with those who used >4.1 mg per day, with a median OS of 8.7 months (95% CI: 6.7–NA) ($n=19$) *vs* 3.2 months (95% CI: 1.2–NA) ($n=4$), respectively ($\chi^2=11.1$, $P=0.0009$; Figure 4B). Although our single-institution cohort has fewer patients compared with the cohorts in the phase III trial, we nevertheless observed a robust segregation of OS in the patient groups, validating the previously observed effect of dexamethasone on patient outcome.

Comparison of patients within the validation cohort with a KPS ⩾70 and dexamethasone usage ⩽4.1 mg per day ($n=19$) to the phase III TTField therapy cohort who used dexamethasone ⩽4.1 mg per day ($n=56$, from Figure 2A) revealed no statistical difference between the two groups, with a median OS of 8.7 months (95% CI: 6.7–NA) *vs* 11.0 months (95% CI: 8.8–16.6), respectively ($\chi^2=2.1$, $P=0.1520$; Figure 4C). We next asked whether important prognostic factors within our cohort varied relative to patients within the phase III cohort by examining the possible effects of age and tumour size. The median age of our

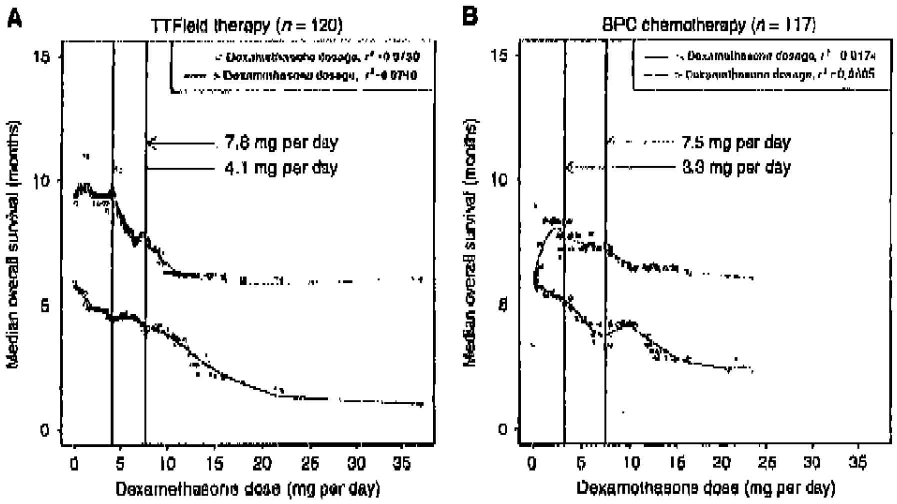


Figure 3. Loess local polynomial regression of median OS vs dexamethasone dose. Dexamethasone was treated as a discrete variable successively and the median OS was plotted for the group ⩽(green) and >(blue) compared with the variable dosage of dexamethasone. Curve fitting was performed using the Loess local polynomial regression. (**A**) In the TTField therapy cohort ($n=120$), there was decremental OS from 4.1 mg per day that reached an inflection point at 7.8 mg per day, after which the rate of OS decrease slowed. (**B**) In the BPC chemotherapy cohort ($n=117$), there was decremental OS from 3.3 mg per day that reached an inflection point at 7.5 mg per day, after which the rate of OS decrease slowed

Table 1. Patient characteristics in the validation cohort and the NovoTTF-100A cohort in phase III trial

Patient characteristics	Validation cohort ($n = 35$)	NovoTTF-100A cohort ($n = 120$)	P-value
Age (range)	57 (30 – 77) years	54 (24–80) years	
Gender			
Male	22 (63%)	92 (77%)	
Female	13 (37%)	28 (23%)	
Karnofsky performance status			
Median	70 (range 50–90)	80 (range 50–100)	
Tumour size, bidimensional			
T1 Gad, median (range) (cm^2)	12.2 (0.3 – 40.6)	14.2 (0.0–56.7)	0.6178
FLAIR, median (range) (cm^2)	35.2 (7.0 – 90.9)	N/A	
Dexamethasone dose			
Median (range) (mg per day)	3.0 (0.0 – 15.0)	4.7 (0.0–37.5)	
Absolute T-cell subsets			
CD3, median (range) (cells per mm^3)	733 (70 – 1458)	N/A	
CD4, median (range) (cells per mm^3)	414 (25 – 788)	N/A	
CD8, median (range) (cells per mm^3)	302 (44 – 1039)	N/A	
Prior therapy			
First recurrence	6 (17%)	11 (9%)	
Second recurrence	10 (29%)	58 (48%)	
Third recurrence	19 (54%)	51 (43%)	
Prior bevacizumab	25 (71%)	23 (19%)	
Outcome			
Overall survival, median (months)	4.3 (95% CI: 3.5–8.7)	7.1 (95% CI: 6.1–8.8)	0.0468

Abbreviations: CI = confidence interval, FLAIR = fluid-attenuated inversion recovery; Gad = gadolinium, N/A = not applicable, TTF = tumour treating alternating electric field

cohort was 57 (range 30–77) years and it is not different from the median age of 54 (range 24–80) years in the TTField-treated cohort from the phase III trial (Stupp *et al*, 2012). Average tumour size in our cohort as measured by gadolinium-enhanced T1-weighted MRI showed a median bidimensional measurement of 12.2 (range 0.30–40.6) cm^2, which is similar to the median bidimensional measurement of 14.2 (0.0–56.7) cm^2 in the TTField-treated phase III cohort ($P = 0.6178$; Table 1). However, 15 of 23 patients (65%) were already on bevacizumab before their neuroimaging studies, possibly interfering with tumour measurement because bevacizumab can reduce vascular permeability in tumours causing decreased gadolinium enhancement (Wong and Brem, 2008). Further, blockade of vascular endothelial growth factor can promote an invasive and diffuse glioblastoma phenotype that result in tumours possessing greater size than can be measured on gadolinium-enhanced T1-weighted MRI (Norden *et al*, 2008; Lu *et al*, 2012). We therefore measured the bidimensional size of the FLAIR abnormality. Indeed, in our cohort, the median bidimensional FLAIR abnormality was 29.6 (range 7.0–60.2) cm^2, which is more than two times the tumour size observed on gadolinium-enhanced T1-weighted MRI in the phase III trial (Stupp *et al*, 2012). As expected, this bevacizumab effect on tumour measurement was corroborated in our entire patient cohort ($n = 38$) by the strong correlation between the size of the gadolinium-enhanced T1-weighted and FLAIR measured bidimensional tumour size among those not on bevacizumab ($r^2 = 0.7333$, $n = 10$; Supplementary Figure 1A), whereas no such correlation was seen among those on bevacizumab ($r^2 = 0.1446$, $n = 27$; Supplementary Figure 1B). Furthermore, we found that patients in our validation cohort who used dexamethasone > 4.1 mg per day ($n = 4$) had a worse outcome compared with the corresponding cohort in the phase III trial ($n = 64$), with a median OS of 3.2 months (95% CI: 1.2–NA) *vs* 4.8 months (95% CI: 3.9–6.0), respectively ($\chi^2 = 6.3$, $P = 0.0121$; Figure 4D). Therefore, our single-institution validation cohort, who had KPS $\geqslant 70$, used dexamethasone $\leqslant 4.1$ mg per day and possessed greater tumour burden, compared favourably with those treated with TTFields therapy in the phase III trial, but those with KPS $\geqslant 70$ but used dexamethasone > 4.1 mg per day probably suffered from a worse outcome compared with the corresponding trial cohort.

Patient immune characteristics and TTField therapy efficacy. Dexamethasone has been associated with profound immunosuppression (Hughes *et al*, 2005; Grossman *et al*, 2011) and it may severely limit a patient's ability to mount an antitumour immune response against the glioblastoma (Zitvogel *et al*, 2008a). Our data clearly demonstrated that dexamethasone doses higher than a threshold level of 4.1 mg per day correlated with a poorer patient outcome during TTField therapy. This finding strongly suggests an immunological component behind the efficacy of this intervention and that factors required for general immune competence may have a role in predicting therapeutic outcome in our patients. We therefore analysed their $CD3^+$, $CD4^+$, and $CD8^+$ T-lymphocyte subsets during the course of their treatment. Using the unsupervised binary partitioning approach described above for dexamethasone dose, we attempted to identify whether there was any threshold for the absolute $CD3^+$, $CD4^+$, or $CD8^+$ T-lymphocyte count, which yielded the greatest statistical difference in OS when used to stratify our patient population. Significantly, this analysis revealed that the median OS of patients with absolute $CD3^+$ $\leqslant 382$ cells per mm^3 was 2.0 months (95% CI: 1.2–NA) ($n = 7$). In contrast, the median OS of those with CD3 > 382 cells per mm^3 was 7.6 months (95% CI: 4.3–13.9) ($n = 22$) ($\chi^2 = 17.8$, $P < 0.0001$; Figure 5A), with the data showing that patient survival was positively correlated with the absolute numbers of $CD3^+$ T lymphocytes. Similarly, we found that patients with absolute $CD4^+$ $\leqslant 236$ cells per mm^3 exhibited a median OS of 2.7 months (95% CI: 1.4–NA) ($n = 9$) as compared with those with $CD4^+$ > 236 cells per mm^3 with a median OS of 8.0 months (95% CI: 4.6–NA) ($n = 20$) ($\chi^2 = 13.4$, $P = 0.0002$; Figure 5B). Furthermore, patients with an absolute $CD8^+$ count of $\leqslant 144$ cells per mm^3 exhibited a median OS of 2.0 months (95% CI: 2.0–NA) ($n = 5$) as compared with 6.8 months (95% CI: 3.9–13.8) ($n = 24$) for those with $CD8^+$ > 144 cells per mm^3 ($\chi^2 = 8.1$, $P = 0.0045$; Figure 5C).

We next asked whether $CD3^+$, $CD4^+$, and $CD8^+$ lymphocyte counts was related to the overall status of the patient's peripheral

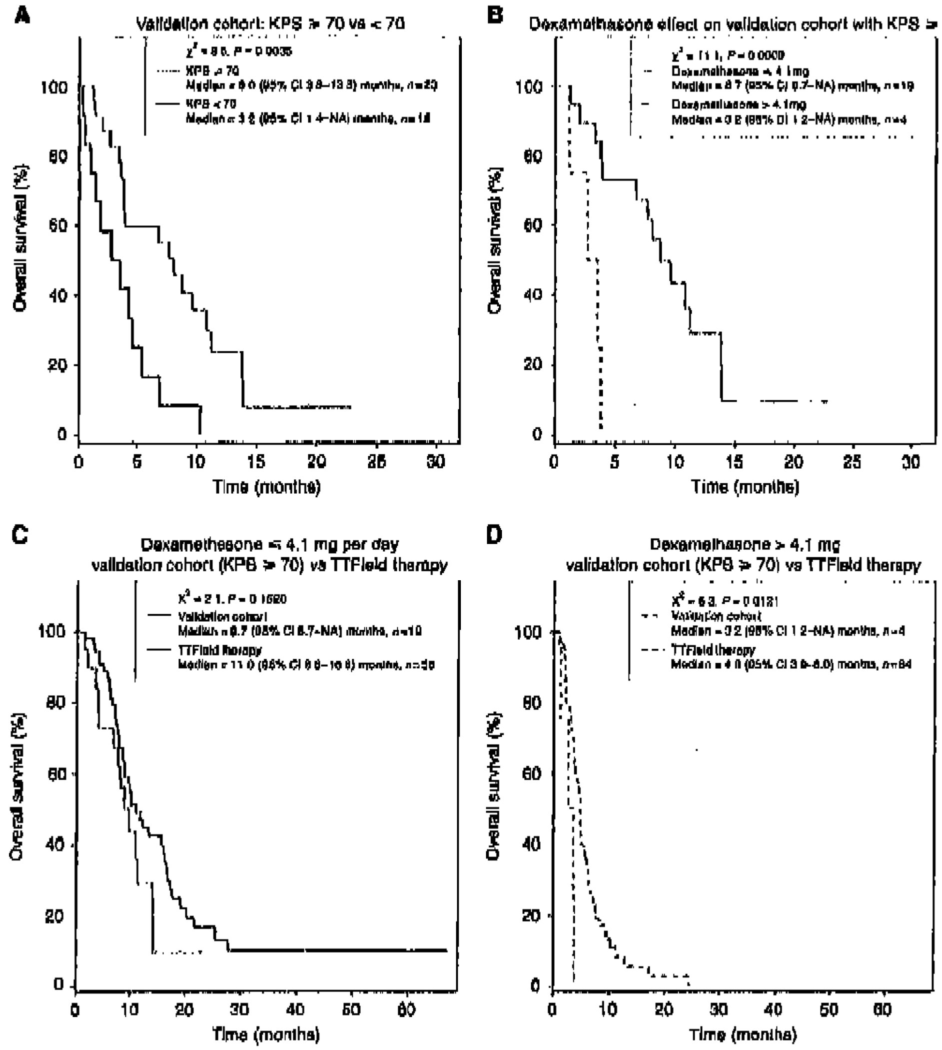


Figure 4. Kaplan–Meier estimates of survival in the validation cohort from a single institution. **(A)** The Kaplan–Meier survival curves for patients with KPS ⩾70 (solid green) *vs* those with KPS <70 (solid black). **(B)** Dexamethasone effect on the cohort with KPS ⩾70 by comparing patients taking dexamethasone ⩽4.1 (solid green) *vs* those taking >4.1 mg per day (dashed green). **(C)** Comparison of the TTField-treated subjects who used ⩽4.1 mg per day of dexamethasone in the phase III trial (from Figure 2A) *vs* the validation cohort with having KPS ⩾70 and taking dexamethasone ⩽4.1 mg per day. **(D)** Comparison of the TTField-treated subjects who used >4.1 mg per day of dexamethasone in the phase III trial (from Figure 2B) *vs* the validation cohort with having KPS ⩾70 and taking dexamethasone >4.1 mg per day.

blood counts and dexamethasone requirement. As expected, there was a correlation between $CD3^+$ and $CD4^+$ cells ($r^2=0.6949$) and between $CD3^+$ and $CD8^+$ cells ($r^2=0.5001$) but not between $CD4^+$ and $CD8^+$ cells ($r^2=0.0733$). However, there was no correlation between white blood cells (WBC) and $CD3^+$ cells ($r^2=0.0053$), WBC and $CD4^+$ cells ($r^2=0.0023$), and WBC and $CD8^+$ cells ($r^2=0.0032$). No correlation was also detected between platelets and $CD3^+$ cells ($r^2=0.2576$), platelets and $CD4^+$ ($r^2=0.2746$), and platelets and $CD8^+$ ($r^2=0.0887$). Similarly, there was no correlation between the daily dexamethasone dose and $CD3^+$ cells ($r^2=0.1888$), dexamethasone and $CD4^+$ cells ($r^2=0.1531$), and dexamethasone and $CD8^+$ cells ($r^2=0.0451$). Taken together, $CD3^+$, $CD4^+$, and $CD8^+$ lymphocyte counts appear to be independent of the peripheral blood counts and dexamethasone dose effect. Therefore, T-lymphocyte counts may serve as an independent measure of immunocompetence in our patients and predict treatment outcome when using NovoTTF-100A.

DISCUSSION

Our previous *post hoc* analysis of responders in the phase III trial comparing NovoTTF-100A monotherapy and BPC chemotherapy for recurrent glioblastoma revealed that dexamethasone and prior low-grade glioma histology were predictors of response (Wong *et al*, 2014). Traditionally, oncologists view dexamethasone's influence on glioblastoma patients from the perspective of its antioedema effect from the tumour (Vecht *et al*, 1994), antiemetic efficacy against emetogenic chemotherapies, infections from its systemic immunosuppressive property (Vecht *et al*, 1994; Hughes *et al*, 2005), and changes in contrast enhancement on computed tomography (Chamberlain *et al*, 1988) or MRI (Ostergaard *et al*, 1999). Because dexamethasone has the potential to produce profound toxicities in patients in large part by suppressing their immune system and it is a clinically modifiable factor, we therefore extended our analysis of possible dexamethasone effect on outcome

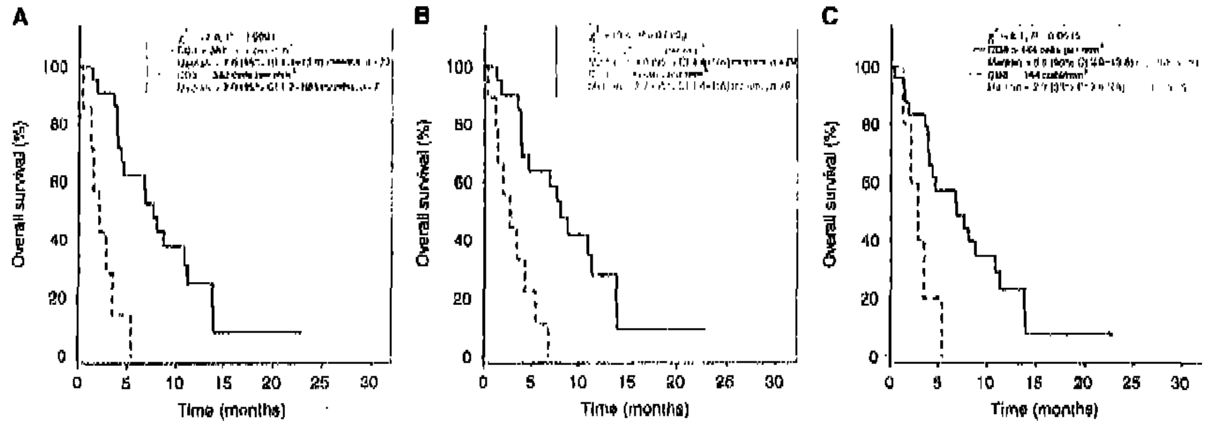


Figure 5. Wilcoxon's rank-sum test of the optimal cutoff T-lymphocyte subsets as determined by an unsupervised binary partitioning algorithm. (A) Median OS of patients with absolute CD3$^+$ $\leqslant$382 vs >382 cells per mm^3 was 2.0 months (range 0.3–5.4) (n = 7) and 7.7 months (range 1.3–22.7) (n = 25), respectively (P = 0.0017). (B) Median OS of patients with absolute CD4$^+$ $\leqslant$236 vs >236 cells per mm^3 was 2.7 months (range 0.3–6.7) (n = 9) and 8.0 months (range 1.3–22.7) (n = 23), respectively (P = 0.0029). (C) Median OS of patients with absolute CD8$^+$ $\leqslant$144 vs >144 cells per mm^3 was 2.7 months (range 1.2–5.4) (n = 5) and 7.6 months (range 0.3–22.7) (n = 27), respectively (P = 0.0313).

to the entire trial cohort. In this study, we have uncovered compelling evidence that dexamethasone counteracted the therapeutic efficacy of TTFields. Further, we also found that its use negatively correlated with survival in the cohort treated with chemotherapy. Our analysis is the first to show this significant impact of dexamethasone on treatment efficacy and patient OS, which is a discrete and unequivocal endpoint in contrast to progression-free survival or response for the conduct of clinical trials for recurrent glioblastomas.

In contrast to commonly used chemotherapeutic regimens, TTField monotherapy does not exert deleterious effects on the immune system, and thus, unlike the chemotherapy-treated cohort, TTField-treated subjects did not receive concurrent immunosuppressive agents other than dexamethasone during the entire trial period. Therefore, this trial provided us with a unique opportunity to examine the interference of dexamethasone on the clinical outcome of patients without the confounding influence of cytotoxic chemotherapies. Given our previous observation that responders from this trial had low dexamethasone usage (Wong *et al*, 2014), we first asked whether we could determine a threshold of dexamethasone exposure below which a benefit in patient survival could be detected within the entire cohort. Using an unsupervised mathematical algorithm, we found that a dexamethasone dose of 4.1 mg per day produced the greatest statistical segregation of OS in the TTField-treated cohort, and subjects who received >4.1 mg per day had a 2.3-fold decrease in median OS compared with those who used $\leqslant$4.1 mg per day. Notably, using this dose level to stratify the control cohort treated with BPC chemotherapy also produced a statistically significant, but less robust, OS segregation, and subjects who received >4.1 mg per day had a 1.5-fold decrease in median OS compared with those who used $\leqslant$4.1 mg per day. Within both cohorts, patients exhibited a decrease in OS starting at about 4.0 mg per day, with progressive decrement until a dosage of 8.0 mg per day, above which there was no further decrease in OS. Therefore, our data indicate that dexamethasone has a generalised and profound interference on treatment efficacy regardless of whether the treatment has non-cytotoxic or cytotoxic properties on the haematopoietic system.

Our analysis strongly indicates that dexamethasone interferes with the efficacy of both TTFields and BPC chemotherapies, the latter of which consisted largely of alkylating chemotherapies. In the sub-populations taking $\leqslant$4.1 mg per day of dexamethasone, 31 subjects treated with TTField monotherapy exhibited a better outcome compared with the corresponding 40 subjects treated with BPC chemotherapy. This small but statistically significant benefit occurred within the first 11 months, after which the OS of the two cohorts overlapped and the benefit from TTField therapy dissipated. In contrast, for the sub-population taking >4.1 mg per day of dexamethasone, 29 subjects treated with TTField monotherapy exhibited a worse outcome relative to the corresponding 22 subjects treated with BPC chemotherapy. Therefore, high dexamethasone dosage appears to negate or counteract the effect of both TTField therapy and BPC chemotherapy. Because the overall trial population in the TTField-treated cohort is only 120, the benefit of treatment in the 31 (26%) subjects taking $\leqslant$4.1 mg per day of dexamethasone is essentially negated by the hindrance caused by the 29 (24%) patients taking >4.1 mg per day of dexamethasone when the populations were not segregated based on dexamethasone burden. This dexamethasone interference with TTField efficacy may explained the improved outcome seen in the trial for newly diagnosed glioblastoma patients (Stupp *et al*, 2014), who were not as severely affected by treatment effects when compared with recurrent glioblastoma patients who had a longer exposure to cytotoxic chemotherapy, dexamethasone, or both.

Our data also indicate that T-lymphocyte subsets may have an important role in the outcome of our validation cohort of patients treated with TTField therapy, with prolonged OS associated with absolute CD3$^+$ >382 cells per mm^3, CD4$^+$ >236 cells per mm^3, and CD8$^+$ >144 cells per mm^3 in an unsupervised analysis. Hughes *et al* (2005) and Grossman *et al* (2011) both showed that dexamethasone induces a drop in CD4$^+$ lymphocyte count, which predisposes glioblastoma patients to infectious complications, and a CD4$^+$ count <200 cells per mm^3 is associated with poor survival. However, we also noted that dexamethasone's immunosuppressive effect also blunted the therapeutic efficacy of TTField therapy and chemotherapy, probably as a result of its global interference with the patient's immune system. This notion is supported by our *in vitro* experiments, which demonstrated that cells attempting to divide in the presence of the TTFields are disrupted in mitosis during the metaphase-to-anaphase transition and experienced aberrant mitotic exit (Gera *et al*, 2015). These cells subsequently exhibited changes consistent with immunogenic cell death and thus were susceptible to immune elimination (Lee *et al*, 2011, 2013). Because subjects that received dexamethasone $\leqslant$4.1 mg per day in the phase III trial exhibited benefit from TTField therapy, the observed benefit is strongly consistent with an

increased immunogenicity of cells affected by TTFields. Furthermore, a number of cytotoxic chemotherapy agents, such as doxorubicin, 5-fluorouracil, and oxaliplatin, can induce either genomic or cytoplasmic stress in the tumour cell leading to immunogenic cell death (Zitvogel *et al*, 2008b). Although the extent of immunostimulatory effects of alkylators, such as lomustine, carmustine, procarbazine, and temozolomide is unknown, dacarbazine has been shown to upregulate NKG2D ligands on tumour cells and thereby target them for immune elimination by natural killer (NK) cells and $CD8^+$ cytotoxic T-lymphocytes (Hervieu *et al*, 2013). Furthermore, alkylating agents have been shown to induce the secretion of ATP and HMGB1, both of which are danger signals that can activate immune responses against dying cells (Zong *et al*, 2004). Lastly, in myeloma patients, dexamethasone can severely block lenalidomide-induced NK cell activation (Hsu *et al*, 2011). Taken together, there is a strong indication from our data that the cytotoxic agents used in the trial against recurrent glioblastomas also act by inducing immune responses against the tumour and that concurrent dexamethasone usage negated this benefit.

There are a number of limitations in the interpretation of our findings. First, our data only allowed us to examine global immunosuppression in our patients but provide no means to assess local immunosuppression within the tumour microenvironment. This local suppression of immune surveillance is thought to be mediated by arginase, regulatory T cells, and myeloid-derived immunosuppressive cells (Fecci *et al*, 2006; Jacobs *et al*, 2010; Raychaudhuri *et al*, 2011). Nevertheless, removal of global immunosuppressive factors is the first step towards successful antiglioblastoma therapy. Second, our T-lymphocyte analysis only measured cells in the adaptive immune system. However, TTField therapy and certain chemotherapy agents could potentially induce an NK cell response against the glioblastoma (Hervieu *et al*, 2013; Lee *et al*, 2013). However, the observed dexamethasone effect on absolute $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes could also negatively influence the activation of other cytotoxic subsets such as NK cells (Hsu *et al*, 2011). Therefore, future analysis of the specific effects of dexamethasone on glioblastoma treatment would need to include the global effect on these cells.

In conclusion, dexamethasone exerted a profound interference on the therapeutic effects of both TTField therapy and BPC chemotherapies. The threshold dose at which dexamethasone was able to be used with minimal interference on these treatments was 4.1 mg per day or lower. In our validation set of TTField-treated patients, the cluster that had the longest OS had $CD3^+ > 382$ cells per mm^3, $CD4^+ > 236$ cells per mm^3, and $CD8^+ > 144$ cells per mm^3. Taken together, these data strongly suggest that the stimulation of immunity against the tumour operates in both of these therapeutic approaches. Future clinical trials for recurrent glioblastoma, as well as other types of brain tumours, may need to take into account the influence of dexamethasone on therapeutic outcome.

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NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality

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KEYWORDS
Glioblastoma
Brain tumour
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Abstract *Purpose:* NovoTTF-100A is a portable device delivering low-intensity, intermediate frequency electric fields via non-invasive, transducer arrays. Tumour Treatment Fields (TTF), a completely new therapeutic modality in cancer treatment, physically interfere with cell division.

Methods: Phase III trial of chemotherapy-free treatment of NovoTTF (20–24 h/day) versus active chemotherapy in the treatment of patients with recurrent glioblastoma. Primary endpoint was improvement of overall survival.

Results: Patients (median age 54 years (range 23–80), Karnofsky performance status 80% (range 50–100) were randomised to TTF alone ($n = 120$) or active chemotherapy control ($n = 117$). Number of prior treatments was two (range 1–6). Median survival was 6.6 versus 6.0 months (hazard ratio 0.86 [95% CI 0.66–1.12]; $p = 0.27$), 1-year survival rate was 20% and 20%, progression-free survival rate at 6 months was 21.4% and 15.1% ($p = 0.13$), respectively in TTF and active control patients. Responses were more common in the TTF arm (14% versus 9.6%, $p = 0.19$). The TTF-related adverse events were mild (14%) to moderate (2%) skin rash beneath the transducer arrays. Severe adverse events occurred in 6% and 16% ($p = 0.022$) of patients treated with TTF and chemotherapy, respectively. Quality of life analyses favoured TTF therapy in most domains.

Conclusions: This is the first controlled trial evaluating an entirely novel cancer treatment modality delivering electric fields rather than chemotherapy. No improvement in overall survival was demonstrated, however efficacy and activity with this chemotherapy-free treatment device appears comparable to chemotherapy regimens that are commonly used for recurrent glioblastoma. Toxicity and quality of life clearly favoured TTF.

1. Background

Glioblastoma is the most prevalent primary malignant brain tumour in adults. Median survival with optimal therapy is only 15 months from diagnosis, and most tumours recur within 9 months of initial treatment.[1] At the time of disease recurrence, treatment options for glioblastoma patients are limited. Repeat surgery may be considered in approximately 20% of patients,[2–4] and re-irradiation is possible in rare circumstances. For most patients chemotherapy is indicated at disease recurrence, with the choice of drug varying greatly. In the United States, bevacizumab has been provisionally approved for recurrent glioblastoma, while the European Medicines Agency (EMEA) rejected the application in the absence of a controlled trial.[5,6] Cytotoxic agents most frequently used are alkylating agents like nitrosoureas (e.g. lomustine [CCNU] or carmustine [BCNU]),[7] procarbazine[8] or re-treatment with temozolomide.[9,10] Response rates are below 10%, progression-free survival rates at 6 months <20%.[7,8] In the absence of an established and satisfactory standard treatment, bevacizumab alone and in combination with irinotecan and experimental treatments are commonly used.[11–13]

Overall survival (OS) from recurrence is commonly short and without effective therapy rarely exceeds 3–5 months.[14–19] In a randomised trial of repeat surgery with implantation of carmustine wafers versus placebo median survival was 6.5 versus 4.7 months.[20] With active therapy, a median survival of 7 months (range 5–9.2 months)[7–10,12,13,21–24] has been reported. A recent randomised comparison of enzastaurin versus lomustine at first recurrence demonstrated a median survival of 7.1 months, with 19% of patients alive and progression-free at 6 months when treated with lomustine.[7] Based on these results active chemotherapy as salvage treatment for patients with recurrent glioma is recommended, which strives to improve survival and quality of life despite inherent chemotherapy-related toxicity.

The NovoTTF-100A system (Novocure Ltd., Haifa, Israel) is a portable device delivering low intensity, intermediate frequency, alternating electric fields (Tumour Treating Fields; TTF) using non-invasive, disposable transducer arrays (Fig. 1A). These fields physically

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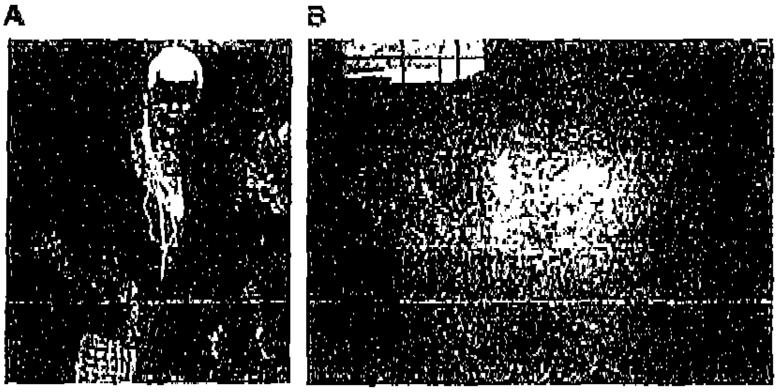

Fig. 1. Female patient wearing the portable NovoTTF-100A device (A). Grade 2 skin rash underneath transducer arrays in a different patient (B). With the patients' permission.

interfere with cell division by causing misalignment of microtubule subunits in the mitotic spindle during the metaphase to anaphase transition[25] and by dielectrophoretic movement of intracellular macromolecules and organelles during telophase.[26,27] This causes failure of cytokinetic furrow formation and resultant mitotic blebbing, leading to the disruption of chromosome segregation and eventual cell death. The exact pathways by which spindle disruption and physical aggregation of macromolecules lead to cell death are unknown. TTF has been tested in several pilot clinical studies[26,28,29] including a small single arm study as monotherapy for recurrent glioblastoma. The results of this pilot trial were promising[26] and served as the basis of this phase III trial comparing NovoTTF-100A monotherapy (TTF) to best active chemotherapy according to the physician's best choice (active treatment control group). This report describes for the first time the efficacy and safety of this entirely novel treatment modality compared to widely accepted active chemotherapies for the treatment of recurrent glioblastoma patients.

2. Methods

2.1. Patient selection

Patients 18 years or older with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma) were eligible following radiologically confirmed disease progression (Macdonald criteria). Patients had a Karnofsky performance status ⩾70% and adequate haematologic, renal and hepatic function (absolute neutrophil count ⩾1000/mm^3; haemoglobin ⩾100 g/L platelet count, ⩾100,000/mm^3; serum creatinine level ⩽1.7 mg/dL (<150 μmol/L); total serum bilirubin level ⩽ the upper limit of normal and liver-function values, <3 times the upper limit of normal). Prior therapy must have included radiotherapy (with and without concomitant and/or adjuvant temozolomide). There was no limit on number or type of prior therapies or recurrences. Patients with infra-tentorial tumour location were excluded, as were patients with implanted electronic medical devices (e.g. pacemaker, programmable ventriculo-peritoneal shunt). All patients provided written informed consent, and the study was approved by the institutional review boards or ethics committees of all participating centres.

2.2. Study design and treatment

Patients were randomised at a 1:1 ratio to receive either TTF monotherapy (without chemotherapy) or the best available active chemotherapy according to the local physician's choice (active control). Randomisation was performed using random block sizes and was stratified by centre and according to whether patients underwent surgery for their latest recurrence prior to trial entry. Assigned treatment had to start within 1 week of randomisation, and was to be continued until disease progression or intolerance.

For patients assigned to the TTF group four transducer arrays were placed on the patient's shaved scalp and connected to a portable, battery or power supply operated device (NovoTTF-100A) which was set to generate 200 kHz electric fields within the brain in two perpendicular directions (operated sequentially). Field intensity was set at >0.7 V/cm at the centre of the brain. Patients were trained on how to operate the device and then continued treatment at home. Treatment was continuous while maintaining normal daily activity. Transducer arrays were replaced by the patients, their caregivers or device technicians once or twice a week. Prior to placement, the scalp was shaved carefully with an electric razor in order to avoid skin wounding, transducer arrays were supplied sterile. Although uninterrupted treatment was recommended, patients were allowed to take treatment breaks of up to an hour, twice per day, for personal needs (e.g. shower). In addition, they were allowed to take 2–3 days off treatment at the end of each 4 weeks of treatment (which is the minimal

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required treatment duration for TTF therapy to reverse tumour growth).[30]

Patients assigned to the active control received chemotherapy at the local investigators discretion. The best available chemotherapy was prescribed according to local practice and depending on prior treatment exposure.

2.3. Patient surveillance and follow up

Baseline examinations included a gadolinium-enhanced magnetic resonance imaging (MRI) of the brain, full blood counts, blood chemistry tests, blood coagulation tests, electrocardiogram (ECG), physical examination including a detailed neurological examination and quality of life (QoL) questionnaire (European Organisation for Research and Treatment of Cancer (EORTC) QLQ C-30).

Patients were followed once a month, including laboratory tests. MRI was repeated every 2 months. QoL questionnaires were completed at baseline and then every 3 months. Tumour response and progression were determined by blinded central radiology review, according to Macdonald criteria.[31] When an MRI could not be obtained, progression was assessed clinically based on neurological status, steroid dosing, adverse events and investigator assessment of progression.

Adverse events were recorded prospectively according to National Cancer Institute Common Toxicity Criteria (NCI CTC V3.0)

2.4. Statistical analysis

The primary end-point was OS. Secondary end-points were progression free survival (PFS), the percentage of patients alive and progression-free at 6 months (PFS6), 1-year survival rate, radiological response rate (RR), QoL and safety. OS and PFS were computed from the day of randomisation until event or censored at last follow-up according to the Kaplan–Meier method, with 2-sided logrank statistics for comparison. The study had an 80 per cent power at a significance level of 0.05 to detect a 60 per cent increase in median OS (hazard ratio for death, 0.63). All analyses were performed using the intent to treat population of all randomised patients, patients lost to follow-up were censored at the time of last contact. A Cox proportional hazards model was used to adjust for confounding baseline variables (continuous and categorical). The survival data were tested for proportional hazards and the assumption of proportionality met. The Cox model was performed in two steps; first, all protocol pre-specified baseline variables were tested directly for interactions with OS; then a reduced model was performed testing the effect of all variables with significant interactions ($p < 0.05$) with OS together on the treatment effect of TTF versus active chemotherapy. Secondary end-points are presented without adjustment. QoL is presented as change from baseline to 3 months for each of the subscale domains and symptom scales of the QLQ-C30 questionnaire.

2.5. Organisational aspects

The trial was registered on www.clinicaltrials.gov, NCT#00379470. The trial was funded and sponsored by Novocure Ltd. Statistical analysis was performed by David Steinberg. The manuscript was written by Roger Stupp and Eilon Kirson, with substantial input by all co-authors. The final manuscript was reviewed and approved by all authors. The statistician and the corresponding author had unrestricted access to all data.

2.6. Role of the funding source

Representatives of the study sponsor were involved in the study design, data collection, data analysis, data interpretation and writing of the report. Data analysis was performed by David Steinberg, a compensated independent biostatistician. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Patients

From September 2006 until May 2009, 237 patients from 28 institutions in 7 countries were randomly assigned to receive TTF monotherapy (120 patients) or active control chemotherapy (117 patients). The baseline patient characteristics were balanced (Table 1). The median age was 54, and a quarter of the patients had undergone some surgical resection of the recurrent tumour prior to enrolment into the trial. More than 80% of patients had failed two or more prior lines of chemotherapy (⩾second recurrence) and 20% of the patients had failed bevacizumab prior to enrolment. Histology was per local pathological diagnosis; in 8% a history of a prior lower grade glioma had been reported (secondary glioblastoma). *Methyl-guanine methyl-transferase* (*MGMT*) gene promoter methylation, an important predictive factor for benefit of temozolomide chemotherapy in newly diagnosed glioblastoma, was not assessed in this trial of patients with recurrent disease.

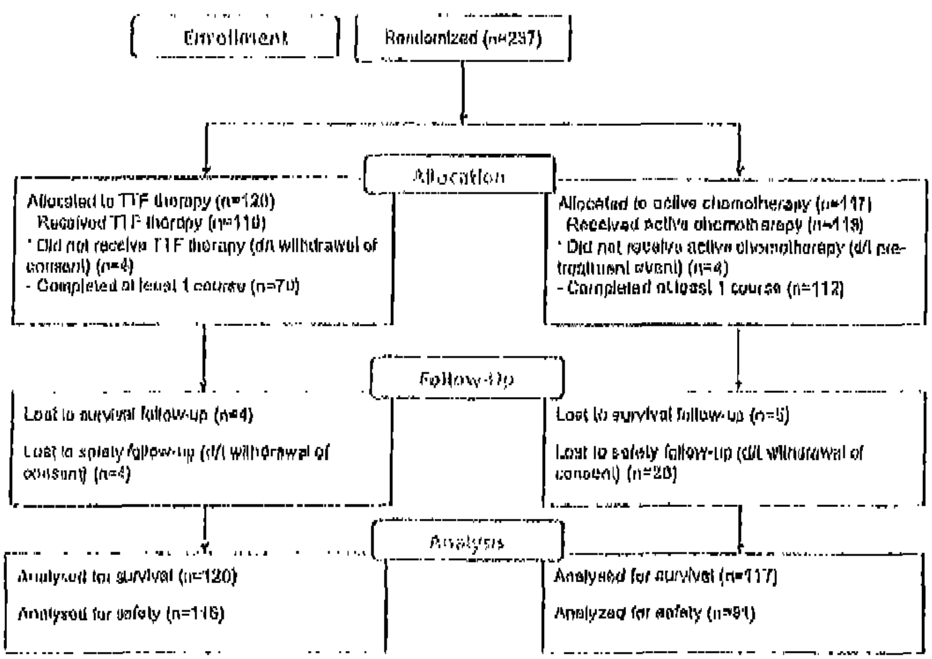
3.2. Patient disposition, treatment and compliance

In the TTF group, 116 of 120 patients (97%) started treatment and 93 patients (78%) completed 4 weeks of therapy (1 cycle). Twenty-seven patients discontinued treatment early, often within a few days, due to non-compliance or inability to handle the device (trial flow

diagram). Four patients had pre-treatment events related to the progressive nature of their disease and never started therapy with the device. In the TTF patients who started treatment (116 patients) mean compliance was measured by downloading a log file from the device, which recorded the actual time TTF therapy was delivered. Median compliance was 86 per cent (range 41–98%) of the time in each treatment month, translating into a mean use of 20.6 h per day.

apy (6.6 versus 6.0 months, respectively). One-year survival proportion was 20% in both groups, the 2- and 3-year survival rates survival rates were 8% (95% CI 4, 13) and 4% (95% CI 1, 8) versus 5% (95% CI 3, 10) and 1% (95% CI 0, 3), for TTF versus active control, respectively (Fig. 1A). The hazard ratio for death was 0.86 (95% CI 0.66, 1.12) in favour of NovoTTF ($p = 0.27$). Adjusting for baseline characteristics using a Cox proportional hazards model did not substantially

trial flow diagram



In the active control group, 113 of 117 patients (97%) started chemotherapy and all but 1 patient completed one full treatment course of the chosen chemotherapy. In four patients disease related adverse events and tumour progression prevented the initiation of the planned chemotherapy, they only received supportive care (hospice care). Twenty-one patients randomised to the control group decided not to return to the investigational site for treatment, thus details on disease progression and toxicity are not available. Most of patients received single agent or a combination chemotherapy regimen containing bevacizumab (31%), or irinotecan (31%), followed by nitrosoureas (25%), carboplatin (13%), temozolomide (11%) or various other agents (5%; Supplementary Table 1).

3.3. Survival, progression and radiological response

At a median follow up of 39 months, 220 patients had died (93%). Median survival was marginally higher in the TTF group compared to active control chemother-

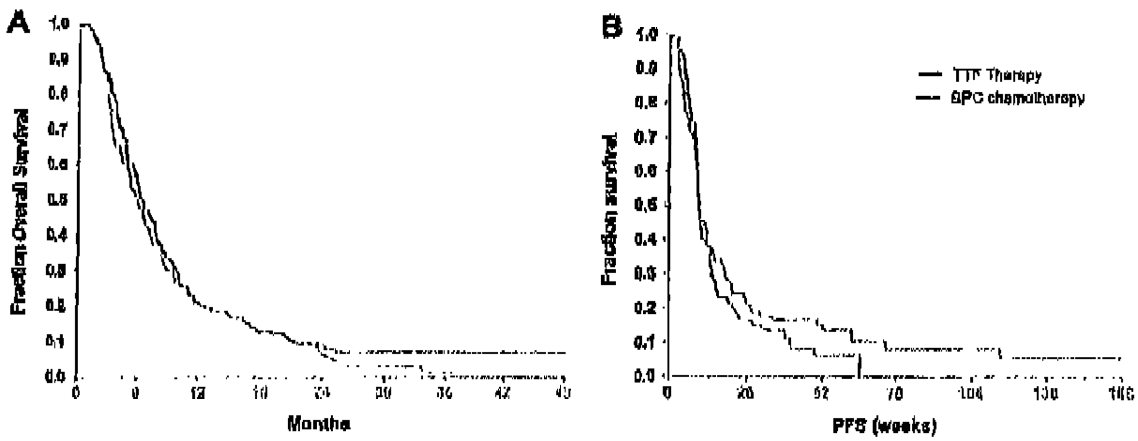
alter the results. In the active chemotherapy control arm of the trial, survival was not significantly affected by the choice of chemotherapy (Cox proportional hazards test; $p = 0.66$).

More objective radiological responses (partial and complete responses) were seen in the TTF group than in the active control chemotherapy group (14 versus 7, respectively), translating into a response rate in evaluated patients of 14.0% (95% CI 7.9–22.4%) versus 9.6% (95% CI 3.9–18.8%), respectively (chi squared $p = 0.19$). All three complete responses were observed in the TTF group. Two exemplary partial responses from TTF are shown in Fig. 3.

The trial had been designed for superiority. Since the control group in the trial is an active chemotherapy control which showed similar efficacy to that seen in previous trials and the device was used as monotherapy it is reasonable to analyse the results also in the context of a non-inferiority analysis. The HR for death in the TTF group compared to the active control chemotherapy group was below 1.0 (0.86; 95% CI 0.66 1.12), indi-

Table 1
Baseline characteristics.

	Tumour Treatment Fields (TTF) ($n = 120$) # pts (%)	Active control ($n = 117$) # pts (%)
Characteristics		
Age, median (range)	54 years (24–80)	54 years (29–74)
Gender		
Male	92 (77)	73 (62)
Female	28 (23)	44 (38)
Histology		
Glioblastoma	100%	100%
Prior lower grade glioma	10 (8)	9 (8)
Karnofsky performance status, median (range)	80% (50–100)	80% (50–100)
Steroid use at enrolment		
Yes	55 (46)	62 (53)
No	55 (46)	49 (42)
Unknown	10 (8)	6 (5)
Largest tumour diameter at randomisation, median (range)	6.1 cm (0–15.2)	5.5 cm (0–16.2)
Interval from initial glioma diagnosis, median (range)	11.8 months (3.2–99.3)	11.4 months (2.9–77.1)
Prior therapy		
1st recurrence	11 (9)	17 (15)
2nd recurrence	58 (48)	54 (46)
3rd or greater recurrence	51 (43)	46 (39)
Surgery		
Debulking before enrolment	33 (28)	29 (25)
Debulking at any stage	95 (79)	99 (85)
Biopsy only	25 (21)	18 (15)
Radiotherapy	100%	100%
With concomitant temozolomide	103 (86)	96 (82)
No concomitant temozolomide	15 (13)	20 (17)
Unknown	2 (1)	1 (1)
Prior adjuvant (maintenance) temozolomide	100 (83)	89 (76)
Median no of cycles	4 (0–19)	3 (0–27)
Prior bevacizumab	23 (19)	21 (18)



At risk	0 m	6 m	12 m	18 m	24 m	30 m	36 m	42 m	48 m
TTF	120	63	24	16	9	7	4	2	1
BPC	117	66	22	14	6	2	1	0	0

0 m	13 w	26w	39w	52w	65 w	78 w	91 w
120	38	19	14	11	6	4	5
117	34	14	10	3	1	0	0

Fig. 2. Overall survival (A) and progression free survival (B) Kaplan–Meier curves.

cating that TTF may be at least equivalent to active chemotherapy.

PFS showed a similar trend in favour of TTF patients as seen for OS (Fig. 1B). Median PFS was 2.2 and

2.1 months for TTF and active control groups, respectively (Fig. 2; HR 0.81, 95% CI 0.60–1.09; log rank $p = 0.16$). PFS6 was 21.4 per cent (95% CI 13.5–29.3) in the TTF group and 15.1 per cent (95% CI 7.8–22.3) in the active control group (chi squared $p = 0.13$).

3.4. Safety and toxicity

As expected from the mechanism of action of TTF therapy and the fact that its delivery is localised to the head, the typical systemic side-effects of chemotherapies were not observed in the TTF treated patients. Mild to moderate (grade 1 and 2) contact dermatitis on the scalp beneath the transducer arrays occurred in 16% of TTF patients (Fig. 1B). This condition was easily treated with topical corticosteroids, resolved completely after treatment, was stopped and did not require substantial treatment breaks.

Patients receiving active control chemotherapy experienced toxicity related to pharmacologic mechanism of the agents used. A list of grade 2–4 adverse events by organ system and adverse event terms seen in more than 2% of patients in either group is presented in Table 2. As expected, there were significantly more gastrointestinal, haematological and infectious adverse events seen in the chemotherapy group than in the TTF group. Severe (grades 3 and 4) toxicity was observed in only 3% of patients.

3.5. Quality of life

Longitudinal Quality of Life (QOL) could be analysed in the patients who remained on study therapy for ⩾3 months and for whom QoL data were available (63 patients, 27%). In the domains of global health and social functioning no meaningful differences between chemotherapy and TTF were observed. However, cognitive and emotional functioning favoured TTF. Physical functioning may be slightly worse with TTF, while role functioning favoured TTF (Fig. 4A). Symptom scale analysis is in accordance to treatment-associated toxicity; appetite loss, diarrhoea, constipation, nausea and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF treatment group (Fig. 4B).

3.6. Treatment after progression

In order to rule out the effect of subsequent treatments on the OS results reported above, we compared the number and type of post-progression treatments patients received after failing the trial therapy. Due to

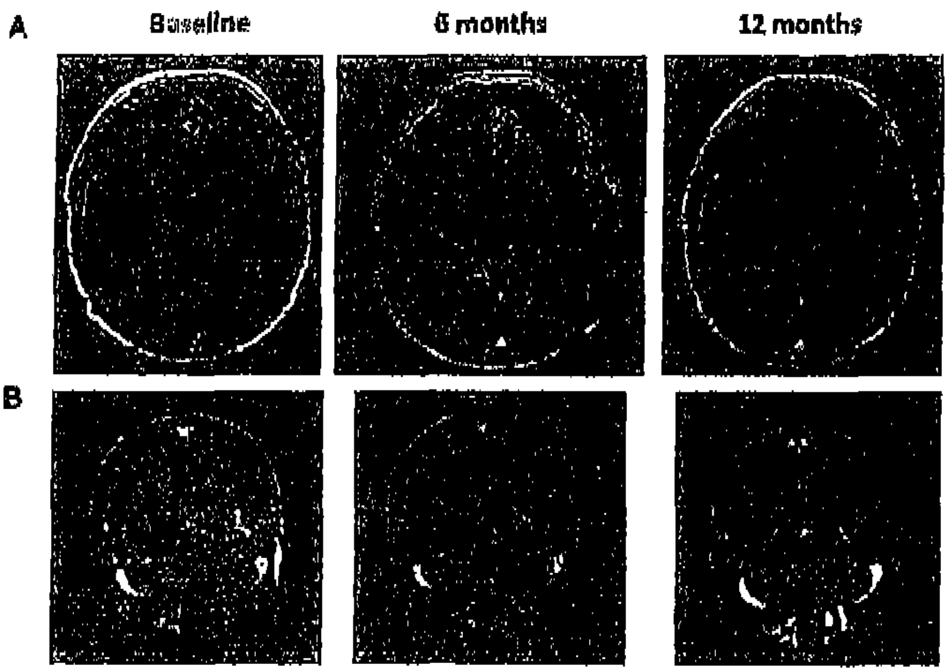


Fig. 3. Exemplary T1 weighted magnetic resonance imaging (MRI) images with gadolinium from two Tumour Treatment Fields (TTF) patients with partial response to therapy. (A) A 48 years old male with prior grade II astrocytoma which transformed to glioblastoma (based on tissue biopsy. The subject progressed 7 months after receiving chemoradiotherapy, and subsequently responded to TTF therapy (partial response at 12 months) and remained stable for an additional 36+ months on TTF. (B) A 55 years old male with primary glioblastoma who recurred for the third time after receiving chemoradiotherapy, adjuvant temozolomide (2 cycles), bevacizumab with irinotecan (3 months) and erlotinib with sorafenib (one cycle). The subject had a partial response to TTF therapy after 4 months of treatment and remained stable for an additional 8 months while on TTF.

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Table 2
Treatment-emergent adverse events ≥ grade 2 by body system.

System	Adverse event term	Tumour Treatment Fields (TTF) ($n = 116$) % (% gr. 3 + 4)	Active control ($n = 91$) % (% gr. 3 + 4)
Haematological		3 (0)	17 (4)
	Leucopenia	0 (0)	5 (1)
	Neutropenia	0 (0)	2 (1)
	Thrombocytopenia	1 (1)[a]	7 (2)
Gastrointestinal disorders		4 (1)	17 (3)
	Abdominal pain	0 (0)	3 (0)
	Diarrhoea	0 (0)	6 (2)
	Nausea/vomiting	2 (0)	7 (0)
General deterioration and malaise		5 (1)	6 (1)
Infections		4 (0)	8 (1)
Skin rash (transducer arrays)		2 (0)	0 (0)
Metabolism and nutrition disorders		4 (1)	6 (3)
Musculoskeletal disorders		2 (0)	5 (0)
Nervous system disorders		30 (7)	28 (7)
	Brain oedema	0 (0)	2 (0)
	Cognitive disorder	2 (1)	2 (1)
	Convulsion	7 (2)	5 (2)
	Dysphasia	2 (0)	1 (0)
	Headache	8 (1)	6 (0)
	Hemianopsia	1 (0)	3 (1)
	Hemiparesis	3 (1)	2 (1)
	Neuropathy peripheral	2 (0)	2 (0)
Psychiatric disorders		5 (0)	4 (0)
Renal and urinary disorders		3 (1)	3 (0)
Respiratory disorders		1 (0)	3 (1)
Vascular disorders		3 (1)	4 (3)
	Pulmonary embolism	1 (1)	2 (2)
	Hypertension	1 (0)	1 (1)
	Deep vein thrombosis	1 (0)	1 (0)

[a] Thrombocytopenia from prior chemotherapy, normalised subsequently.

the very advanced stage they were recruited to the study (most patients were at their second or subsequent recurrence), only 5.8% of the TTF-treated patients and 10.3% of the chemotherapy-treated patients received subsequent salvage antitumour therapy (chi square $p = 0.24$) (mainly bevacizumab, irinotecan, nitrosoureas and temozolomide). The majority of patients received only supportive care once tumour progression developed.

4. Discussion

Tumour treatment with alternating electrical fields that interfere with the metaphase to anaphase transition in dividing tumour cells is an entirely novel cancer treatment modality. We report the first prospective, randomised, controlled study using this new treatment modality in the most aggressive primary brain tumour. Although glioblastoma diffusely infiltrates the brain, it almost never metastasises and is thus amenable to a loco-regional therapy.

Prognosis of patients with recurrent glioblastoma is poor, and chemotherapy is usually recommended. Depending on prior treatments and treatment centre expertise, variable chemotherapy agents alone or in combination are commonly prescribed. Our randomised trial compared this standard chemotherapy per local practice (active treatment control group) with TTF in a prospective, multicentre phase III trial. Although the trial did not reach its primary end-point of improved survival compared to active chemotherapy, this new minimally invasive and chemotherapy-free local treatment modality demonstrated a statistically non-significant increased response rate (14 versus 9.6%, $p = 0.19$), an improved PFS6 rate (21% versus 15%, $p = 0.13$), and a trend towards reduction of the risk of death (hazard ratio 0.86, 95% CI 0.66–1.12, $p = 0.27$), as well as sustained improvement in QoL.

These results cannot be explained by subsequent salvage chemotherapy, as few patients received additional therapy after failure of protocol treatment. Importantly, the majority of our patients were recruited to the trial at an advanced stage of the disease, after failure of two or more chemotherapy agents, while other trials in recurrent glioblastoma usually only enrol patients at first recurrence. It is also notable that 20% of patients had failed prior bevacizumab therapy, a population that usually fares poorly with most subsequent treatments.

One limitation of the study was the absence of a placebo or treatment-free control arm. In the setting of advanced disease and chemotherapy considered indicated and effective, such a control would hardly have been acceptable to patients and physicians alike. Fur-

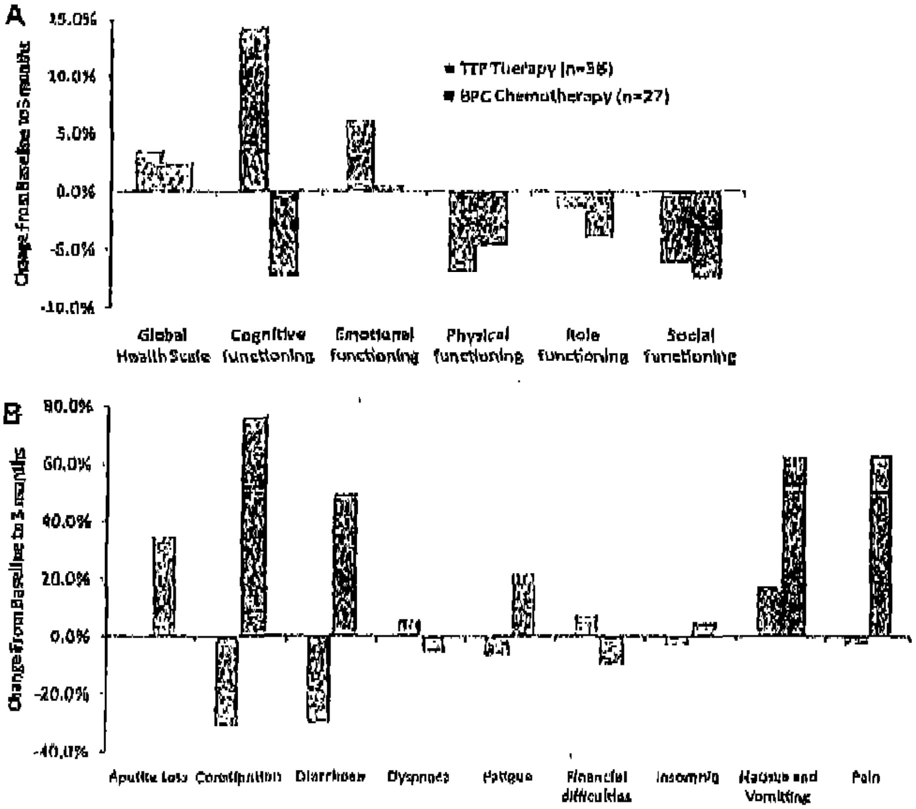

Fig. 4. QLQ C30 longitudinal change from base to 3 months. (A) General functional scales (an increase in percentage corresponds to an increase in QOL). (B) Symptom scales (an increase in percentage corresponds to a decrease in QOL).

thermore, chemotherapy with lomustine has shown superior efficacy versus investigational treatments in two recent randomised trials. And based on high response rates and prolonged survival compared to historical controls bevacizumab has received accelerated Food and Drug Administration (FDA) approval. Furthermore, the observation of objective responses in 14 patients with NovoTTF alone (median time since end of prior RT 7 months, thus unlikely to be all pseudoprogression) strongly suggests singular activity of this device.

Another limitation is the somewhat heterogeneous patient population, with patients included after progression of one or several lines of prior chemotherapy. This underscores the demand from patients for further treatments, even when the expected benefit of a 2 months prolongation in PFS may appear modest. In the ongoing randomised phase III trial for newly diagnosed glioblastoma, only patients non-progressive after completion of chemoradiation are eligible (Novocure EF-14, www.clinicaltrials.gov, NCT#00916409).

As expected with a local treatment, toxicity was limited to skin irritation from transducer arrays (Fig. 1B). After proper instructions, most patients became independent in handling this device and replacing transducer arrays, allowing them to be ambulatory and even going to work. Despite the inconvenience of carrying and using the device almost permanently, compliance was high and patients reported improvement in QoL in the absence of chemotherapy related toxicities.

In vitro and animal experiments suggest enhanced effect when TTF is combined with chemotherapy.[28,32] We therefore initiated a subsequent randomised phase III trial currently enrolling newly diagnosed glioblastoma patients after completion of standard radiochemotherapy, parallel to starting the adjuvant or maintenance temozolomide chemotherapy. Patients randomised to the experimental arm will receive TTF in addition to maintenance temozolomide (www.clinicaltrials.gov, NCT#00916409).

Based on the result of this trial TTF therapy has recently been approved in the US and Europe for the treatment of recurrent glioblastoma (www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm251669.htm).

The universal anti-cancer effect of TTF may be applicable to other solid tumour types, alone or in combination with chemotherapy. In particular, in a situation of morbidity induced by a heavy local tumour burden, and in conditions where further radiotherapy is not an option, this non-invasive treatment may allow for a clinical benefit and will substantially expand our treatment armamentarium.

Conflict of interest statement

Eilon Kirson and Uri Weinberg are employees of Novocure Ltd., and have stock options in the company.

Herwig Kostron has received honoraria from Novocure Ltd.

Yoram Palti is the inventor of the Novo-TTF principle. He received consulting honoraria and travel support by Novocure Ltd.

Nina Paleologos has served on advisory boards and speakers bureau to Genentech, Merck & Co (previously Schering-Plough).

Susan Pannullo has received research grants from Novocure, NTI Pharma, Eisai, Immunocellular and Parexel, and honoraria for lectures from Merck & Co (previously Schering-Plough).

Zvi Ram is a board member for Novocure, and received consultancy honoraria.

Jeffrey Raizer has received research support from Novocure Ltd., performed consultancy for Merck and Genentech/Roche, and lectures on behalf of Merck & Co, Genentech and Enzon.

David Schiff has performed consultancy for Genentech and Tau Pharmaceuticals.

Andrew Sloan has provided consultancy to Genentech/Roche, Real Bio Inc., Nanfiber Solutions, Surgical Theatre and Monteris Medical Inc.

Roger Stupp has served on scientific advisory boards for Merck-Serono, Roche, Actelion, MDxHealth (previously OncoMethylomeSiences) and Merck and Co (previously Schering-Plough).

Manfred Westphal has received consultancy honoraria from Roche, OncoScience and Ark Therapeutics.

Eric T. Wong has received research support from Novocure Ltd.

The following authors declare no potential conflict of interest: Jeffrey Bruce, Lawrence Chin, Rees Cosgrove, Vladimir Dbaly, Herbert Engelhard, Philip Gutin, Volkmar Heidecke, Silvia Hofer, Andrew Kanner, Lara Kunschner, Joseph Landolfi, Frank Lieberman, Marc Malkin, Maximilliam Mehdorn, Franz Payer, Martin Smrcka, David Steinberg, J. Lee Villano, and Robert Weil.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2012.04.011.

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EXPERT REVIEWS

NovoTTF-100A: a new treatment modality for recurrent glioblastoma

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NovoTTF-100A (Novocure Inc., Haifa, Israel) is a first-of-a-kind device approved by the US FDA for the treatment of recurrent glioblastoma. It works by emitting a low-intensity, intermediate-frequency (200 kHz), alternating electric field administered via insulated transducer arrays applied onto the scalp. The electric field penetrates the brain and inhibits the growth and proliferation of glioblastoma by interfering with tumor cell mitosis at anaphase. Results from a Phase III clinical trial indicate that the efficacy of NovoTTF-100A is equivalent to standard-of-care chemotherapy. The side effect profile favors device-treated patients, obviating typical toxicities associated with chemotherapy or targeted drugs, and results in improvements in their quality of life. NovoTTF-100A is a new modality of cancer treatment that offers equivalent efficacy, but less toxicity, to recurrent glioblastoma patients when compared with existing treatments.

KEYWORDS: chemotherapy • electric field • glioblastoma • NovoTTF-100A • tumor-treating field

Overview of the market

Despite continuing research in drug treatments for glioblastomas, median patient survival remains a dismal 14.6 months from the time of initial diagnosis using combined radiation and chemotherapy [1]. Fewer than 10% of patients survive to the 5-year time point [2]. At the time of glioblastoma recurrence or progression, the overall survival (OS) of patients is even worse – typically 6 months or less [3]. The only US FDA-approved medical treatment for recurrence is bevacizumab, but this drug has never been tested in a Phase III clinical trial. Current salvage treatment with bevacizumab prolongs only the progression-free survival (PFS), but not OS, and the tumor invariably progresses in an infiltrative pattern, causing neurological deficits and eventual death [4,5]. Both bevacizumab and cytotoxic chemotherapies have serious side effects that include hemorrhage, thromboembolism, infection, hypertensive crisis, renal failure, diarrhea, nausea and vomiting [4–6]. Therefore, there is a great unmet need for novel therapies that have new mechanisms of action against glioblastoma and a more favorable toxicity profile.

Introduction

NovoTTF-100A (Novocure Inc., Haifa, Israel) is a novel class of therapeutic device being used for the treatment of recurrent glioblastoma. It works by emitting low-intensity, intermediate-frequency (200 kHz), alternating electric fields administered by insulated transducer arrays to inhibit the growth and proliferation of intracranial glioblastomas [7]. This device, which consists of the transducer arrays, electric field generator (set at a frequency of 200 kHz) and battery (Figure 1), was approved for use by the FDA on 8 April 2011 [101]. This review summarizes its mechanisms of action, Phase III efficacy and safety data, and current use in clinical practice.

Mechanism of action

NovoTTF-100A exerts its anti-tumor effect on glioblastoma cells by interfering with mitosis at anaphase. In synchronized cell culture, such a tumor-treating electric field (TTField) first disrupted cytokinesis and then impaired chromosome separation from the metaphase plates [8]. Biochemical assays also confirmed that these cells had already transited from metaphase to anaphase [8]. Immunofluorescence of treated cells demonstrated lagging chromosomes, dispersion of chromosomes, chromosome decondensation in the absence of cytokinesis, and asymmetric chromosome segregation [8,9]. Exposed cells showed no p53 induction, suggesting that cell death was mediated via a p53-independent

Figure 1. The NovoTTF-100A device setup. Left panel: The NovoTTF-100A device. Right panel: Two opposing pairs of transducer arrays (A) are applied to the scalp and the cables are linked to the connection box (B). The connection box is then attached to the electric field generator (C), which is connected to a power supply (D). The entire set up weighs approximately 7 lbs.

mechanism [8]. Furthermore, susceptibility to TTField is cell type dependent. Both glioma cells from rats (F-98) and humans (U87 and U118) have a significantly decreased growth rate when exposed to TTField [9]. The best result appears to occur at an intensity of 2.25 V/cm and a frequency of 200 kHz [9]. Taken together, TTField represents a new modality of anticancer treatment via a mechanism that differs from conventional radiotherapy, cytotoxic chemotherapies or targeted kinase inhibitors. However, additional research is needed to determine the effect on postmitotic neurons and glia, as well as dividing progenitor cells, within the brain.

Clinical efficacy

NovoTTF-100A underwent initial testing in a pilot trial of ten patients with recurrent glioblastoma [7]. The results showed that the median time to disease progression was 26.1 weeks (range: 3.0–124.0 weeks), the PFS at 6 months (PFS6) was 50% (95% CI: 23–77%), and the median OS was 62.2 weeks (range: 20.3–124.0 weeks) [1]. There were two durable responses, including two patients with complete and partial responses lasting 45.3+ weeks and 30.3+ weeks, respectively [7]. These preliminary data compared favorably to benchmark outcomes from conventional cytotoxic chemotherapies, which had a response rate of 9%, PFS6 of 15%, median PFS of 9.0 weeks, and a median OS of 25.0 weeks (95% CI: 21–28 weeks) [3].

NovoTTF-100A was subsequently compared to best standard of care (BSC) chemotherapy for recurrent glioblastoma after initial temozolomide chemoradiation in a prospective, randomized, open-label Phase III clinical trial. Among the 28 centers in the USA and Europe, 237 individuals were randomized to NovoTTF-100A alone (120 subjects) or BSC (117 subjects) [10,11]. The primary end point was OS and secondary end points included PFS, PFS6, 1-year survival rate, objective radiological response, quality of life and safety. All analyses were performed on the intent-to-treat population, and Kaplan–Meier OS and PFS were computed from the time of randomization until event or censoring at last follow-up. The trial was powered at 80%, with a significance of $p \leq 0.05$ and a hazard ratio (HR) for death of ≤0.67. The median age, Karnofsky Performance Score and other clinical characteristics were balanced between the two cohorts, with the exception of slightly larger tumor size in the NovoTTF-100A group versus the BSC group, at a median size of 6.1 cm (range: 0.0–15.2 cm) and 3.5 cm (range: 0.0–16.2 cm), respectively (Table 1) [10,11]. BSC chemotherapies chosen by the treating physician included single-agent or combination irinotecan (31%), bevacizumab (31%), BCNU/CCNU (25%), carboplatin (13%), temozolomide (11%), combination procarbazine, CCNU and vincristine (9%), etoposide (5%), imatinib (2%), hydroxyurea (1%), or nothing (3%) [10,11]. In the intent-to-treat population, the median OS was 28.6 versus 26.0 weeks (HR: 0.86; 95% CI: 0.66–1.12), the median PFS was 9.5 versus 9.1 weeks (HR: 0.84, 95% CI: 0.64–1.13), and the median PFS6 was 21 versus 15% for NovoTTF-100A and BSC chemotherapy, respectively (Figure 2) [10,11]. The data indicate that NovoTTF-100A has an equivalent efficacy when compared to salvage cytotoxic chemotherapies and targeted drugs for recurrent glioblastoma. Interestingly, patients who failed bevacizumab and then enrolled to receive NovoTTF-100A (n = 23) had a significantly longer survival than those who received BSC chemotherapy (n = 21), at 19.1 versus 13.4 weeks ($p < 0.02$), respectively [12].

Safety & tolerability

The side effect profile favors NovoTTF-100A treatment significantly more than BSC. Notably, there were only 3 versus 17% hematological toxicities, 4 versus 17% gastrointestinal side effects, and 4 versus 8% infections at grade 3 or 4 severity in the NovoTTF-100A versus BSC cohorts, respectively [10,11]. Other systemic toxicities were well-balanced between the two groups. However, scalp irritation from transducer array placement did occur at a higher frequency, with 17% grade 1 and 2 skin rash in the NovoTTF-100A subjects when compared with 0% in those treated with BSC chemotherapy [10,11]. However, none of the device-treated patients experienced skin toxicity higher than grade 2. Additional self-reported quality-of-life analysis by EORTC QLQ C-30 showed positive scores from NovoTTF-100A usage due to improved cognitive function, decreased constipation and diarrhea complications, as well as absence of pain [11,12].

Use in practice

Certain medical conditions are contraindicated in NovoTTF-100A usage and may post unknown risks to patients. First, it is inadvisable to prescribe this device to patients with active implanted medical devices, such as cardiac pacemakers, defibrillators, deep-brain stimulators, vagus nerve stimulators and

Table 1. Baseline characteristics of subjects enrolled in the Phase III NovoTTF-100A trial for recurrent glioblastoma.

Age, median (range)	54 (24–80) years	54 (29–74) years
Gender:		
– Male	92 (77%)	73 (62%)
– Female	28 (23%)	44 (38%)
Histology:		
– Primary glioblastoma	110 (92%)	108 (92%)
– Secondary glioblastoma	10 (8%)	9 (8%)
Karnofsky performance status, median (range)	80 (50–100)	80 (50–100)
Corticosteroid use at the time of enrollment:		
– Yes	55 (46%)	62 (53%)
– No	55 (46%)	49 (42%)
– Unknown	10 (8%)	6 (5%)
Maximum tumor diameter at randomization, median (range)	6.1 (0.0–15.2) cm	5.5 (0.0–16.2) cm
Time from initial gliomas diagnosis, median (range)	11.8 (3.2–99.3) months	11.4 (2.9–77.1) months
First recurrence	11 (9%)	17 (15%)
Second recurrence	58 (48%)	54 (46%)
Third or greater recurrence	51 (43%)	46 (39%)
Surgery:		
– Debulking surgery prior to enrollment	33 (28%)	29 (25%)
– Debulking at any stage	95 (79%)	99 (85%)
– Biopsy only	25 (21%)	18 (15%)
Radiotherapy:	120 (100%)	117 (100%)
– Radiotherapy with concomitant temozolomide	103 (86%)	96 (82%)
– Radiotherapy without concomitant temozolomide	15 (13%)	20 (17%)
– Unknown	2 (1%)	1 (1%)
Prior adjuvant (maintenance) temozolomide	100 (83%)	89 (76%)
Median number of cycles	4 (0–19)	3 (0–27)
Prior bevacizumab use	23 (19%)	21 (18%)

Data taken from [11].

programmable ventriculoperitoneal shunts. These devices may cause reciprocal electromagnetic interference, induction or both, and the extent of this risk is unknown. Second, patients with major skull defects cannot receive this treatment. For example, those with a missing section of the calvarium may experience elevated electric field strength on the brain. However, those with healed burr holes and craniotomy sutures can receive this treatment without complications. Third, metals within the brain are also contraindicated because NovoTTF-100A has not been tested in patients with bullet fragments or aneurysm clips in their head. Last, those with hypersensitivity to hydrogel, which is used as a conductive interface between the transducer array disks and the scalp, may not be able to receive this treatment.

Pretreatment evaluation consists of baseline history, physical examination (including evaluation of skin integrity on the scalp), blood work and gadolinium-enhanced head MRI. The MRI images are used to construct a mapping diagram for placement of the transducer arrays. Typically, there are two pairs of opposing arrays, which are separately color coded (Figure 1). The wires of the arrays are then connected to the electric field generator and power supply (Figure 1). The patient's hair is then shaved off with an electric shaver instead of a razor in order to avoid superficial

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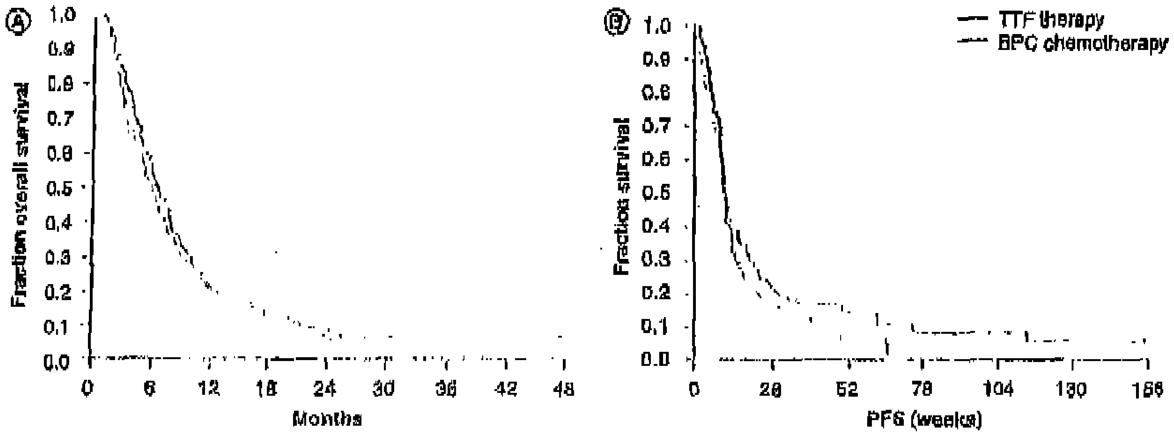

At risk	0 m	6 m	12 m	18 m	24 m	30 m	36 m	42 m	48 m	0 m	13 w	26 w	39 w	52 w	65 w	78 w	91 w
TTF	120	63	24	15	9	7	4	2	1	120	38	19	14	11	6	4	3
BPC	117	56	22	14	6	2	1	0	0	117	34	14	10	3	1	0	0

Figure 2. Data from a Phase III NovoTTF-100A trial for recurrent glioblastoma. (A) Kaplan–Meier curves showing equivalent overall survival between the NovoTTF100A therapy group and the BPC active control. **(B)** Kaplan–Meier progression-free survival curves showing a greater number of subjects with disease stabilization in the NovoTTF-100A-treated group than BPC active control: four subjects without disease progression at 78 weeks and three at 91 weeks versus none in the control.
BPC: Best physician choice; m: Months; PFS: Progression-free survival; w: Weeks.
Reproduced with permission from [11].

ears. The scalp is then cleaned with alcohol prior to application of the arrays. This procedure typically requires the help of another individual and it is necessary to bring a family member or assistant to learn array placement and operation of the NovoTTF-100A device. Follow-up clinic visits are scheduled monthly in the first 3 months and then every 2 months thereafter. Gadolinium-enhanced head MRI is performed once every 2 months for monitoring the status of glioblastoma during treatment.

The efficacy of NovoTTF-100A on brain tumors other than glioblastoma is unknown. However, other gliomas may respond to the same frequency (200 kHz) emitted by the NovoTTF-100A device, based on published preclinical data. However, it is still unknown whether or not TTField at 200 kHz would be effective in controlling metastatic brain tumors because the optimal frequency for specific metastasis may be different. For example, in preclinical cell culture melanoma was most sensitive at a frequency of 120 kHz [9].

Regulatory affairs

NovoTTF-100A is currently approved by the FDA and the EMA for the treatment of recurrent or progressive glioblastomas.

Conclusion

NovoTTF-100A is a novel therapy for the treatment of recurrent glioblastoma. It emits TTField that interferes with dividing tumor cells at anaphase. The clinical trial results indicate that it has comparable efficacy and less toxicity, when compared to conventional drug treatments in the recurrence setting.

Expert commentary

The Phase III clinical trial demonstrated comparable, but not superior, efficacy when compared to conventional drug treatments. This result is likely to be influenced by a number of factors. First, the population of patients with recurrent glioblastomas has neurological deterioration and death within a shorter time than those with newly diagnosed disease. As a result, these patients may deteriorate early and therefore their tumors may not receive enough exposure to NovoTTF-100A treatment. Unlike conventional cytotoxic chemotherapies that have a biological effect lasting the entire duration of the treatment cycle (typically 4–6 weeks), the TTField needs to be applied continuously otherwise the anti-tumor effect would disappear as soon as the generator is switched off. Consistent with this reasoning, the per-protocol analysis of the Phase III trial data, in which patients who received less than 4 weeks of NovoTTF-100A treatment were removed from analysis, showed that NovoTTF-100A offered a statistically significant survival advantage when compared to BSC chemotherapy. Second, compared to newly diagnosed glioblastomas, recurrent glioblastomas have additional genetic alterations making them more resistant to treatment [13,14]. Therefore, NovoTTF-100A may have a greater benefit to newly diagnosed patients than those with recurrent disease. A Phase III clinical trial is currently underway investigating the efficacy of NovoTTF-100A with temozolomide chemoirradiation compared to standard temozolomide chemoirradiation for newly diagnosed glioblastoma. Last, NovoTTF-100A does not appear to have overlapping toxicity with conventional drug treatments [10,11]. Therefore,

combining it with cytotoxic chemotherapies or targeted agents can potentially result in increased efficacy and without added toxicity. The pivotal Phase III trial did include patients after failure of polifeprosan 20 with carmustine implant (Gliadel wafer) [11]. However, for patients who have undergone wafer implantation, it would be best to withhold the use of NovoTTF-100A until complete dissolution of the wafer, which typically occurs in 4 weeks. However, more preclinical data are needed in order to find the optimal NovoTTF-100A and drug combinations before they can be applied in a clinical trial setting.

Five-year view

In the next 5 years, more preclinical studies are needed in order to determine the mechanisms of TTField's action on tumor cells. The results would most likely offer ideas for investigator-initiated clinical research that would help to maximize the efficacy of NovoTTF-100A against glioblastomas. This will most likely be accomplished by the addition of drugs that have synergistic or additive activities. A logical combinatorial treatment would include NovoTTF-100A and bevacizumab because these two therapies do not have overlapping toxicity and both are approved by the FDA for the treatment of recurrent glioblastomas. Furthermore, the device could also be used to treat patients with metastatic brain tumors. However, more preclinical and clinical research is needed to support its use in these patients, as well as the specific type of metastatic brain tumor that shows sensitivity to TTField.

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Key issues

- NovoTTF-100A (Novocure Inc., Haifa, Israel) emits a low-intensity, intermediate-frequency (200 kHz) alternating electric field that treats recurrent glioblastomas.
- NovoTTF-100A exerts its anti-tumor effect on glioblastoma cells by interfering with mitosis at anaphase.
- NovoTTF-100A treatment offers comparable efficacy when compared to conventional drug treatments, including bevacizumab, for recurrent glioblastoma.
- The toxicity profile favors NovoTTF-100A over conventional drug treatments.

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Website

101. US FDA News Release 4 April 2011: FDA approves new medical device for form of brain cancer. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm251669.htm

By Philip H. Gutin, MD, and Eric T. Wong, MD

Overview: Tumor treating fields (TTF) therapy is a novel antimitotic, electric field–based treatment for cancer. This nonchemical, nonablative treatment is unlike any of the established cancer treatment modalities, such as surgery, radiation, and chemotherapy. Recently, it has entered clinical use after a decade of intensive translational research. TTF therapy is delivered to patients by a portable, battery-operated, medical device using noninvasive transducer arrays placed on the skin surface surrounding the treated tumor. TTF therapy is now a U.S. Food and Drug Administration (FDA)–approved treatment for patients with recurrent glioblastoma (GBM) who have exhausted surgical and radiation treatments. This article will introduce the basic science behind TTF therapy, its mechanism of action, the preclinical findings that led to its clinical testing, and the clinical safety and efficacy data available to date, as well as offer future research directions on this novel treatment modality for cancer.

THE DEFINITION of the electric field is attributed to Michael Faraday in the 1830s and was later formulated by James Clerk Maxwell in his electromagnetic theory in 1860.[1] It is a field of electric forces that surround a source charge. When a test charge is placed within an electric field, a force acts on it. Negative charges attract positive charges, while similar signed charges repel each other. As seen in Fig. 1A, an electric field surrounding a source charge can be described using diverging lines of force. The closer the test charge is to the source charge, the closer the lines of force are to each other, which represents higher field intensity.

To understand the effects of electric fields within cells, it is important to introduce three definitions. First, electric fields can be uniform or nonuniform. A uniform electric field is represented by parallel lines of force (Fig. 1B). A nonuniform electric field is represented by converging or diverging lines of force (Fig. 1A and 1D). Second, an electric field can be a constant field or a time-varying field, resulting in electrostatic or electrodynamic phenomena, respectively. In a constant field, the source charges remain the same over time. A test charge will move in one direction within a constant electric field toward the oppositely charged source (Fig. 1B). In a time-varying or alternating electric field, the charge of the sources alternates over time (Fig. 1C). Third, the test charge can be an electric charge or an electric dipole (an element with a positive charge on one end and a negative charge on the opposite end). An electric charge will move back and forth, while a dipole will rotate within an alternating uniform electric field and align with the direction of the field. In a nonuniform converging electric field, both dipoles and charges move in the direction of the higher field intensity through a process known as dielectrophoresis (Fig. 1D).

Mechanism of Action of TTF Therapy

Over 100 years after Maxwell's original publication, Yoram Palti, MD, PhD, hypothesized that properly tuned alternating electric fields at physiological intensities (i.e., 1–3 V/cm) would disrupt the mitotic process of dividing cancer cells.[6,7] Dr. Palti hypothesized and subsequently demonstrated in vitro that at frequencies between 100 and 300 kHz, alternating electric fields disrupt the formation of the mitotic spindle during metaphase and lead to dielectrophoretic movement of charged and/or polar molecules and organelles during anaphase and telophase, disrupting normal cytokinesis and leading to apoptosis.[7,8] According to this model, the first mechanism of action is explained by the fact that the tubulin subunits are one of the most polar molecules in the cell. These tubulin subunits align in the direction of the applied electric field (Fig. 2A), interfering with the normal polymerization of the mitotic spindle, which results in formation of abnormal mitotic figures in vitro.[5] The second mechanism of action is explained by examining the change in shape of the electric field within a dividing cell from anaphase to telophase. When the cell division axis is aligned with the direction of the electric field, the field lines that enter the cell at one end converge at the cytokinetic furrow between the developing daughter cells and then diverge on the opposite side (Fig. 2B). This nonuniform electric field within the cell generates dielectrophoretic forces that act on polar and charged elements in the cell, pushing them toward the cytokinetic furrow leading to violent blebbing of the plasma membrane.[3] This finding was also validated by researchers from Beth Israel Deaconess Medical Center and may be mediated by improper placement of the contractile elements that form the cytokinetic ring on anaphase entry.[4]

Preclinical Studies of the Antitumor Effects of TTF Therapy

Between 2004 and 2010, a series of publications and conference presentations addressed the issue of the applicability range of TTF therapy to different in vitro and in vivo cancer models either alone or in combination with standard chemotherapy.[3,6-8] Tables 1 and 2 summarize the state-of-the-art preclinical research with TTF therapy. TTF therapy has been shown to effectively inhibit cancer cell growth in various cell lines in vitro (Table 1). This effect was clearly dose (field intensity) dependent in the range of 1 to 3 V/cm.[7] The optimal frequency for the inhibitory effect of TTF therapy differed between cell types and was inversely related to cell size (Table 1; e.g., glioma cell cultures at 200 kHz[4,5]). In addition, based on the directional nature of TTF

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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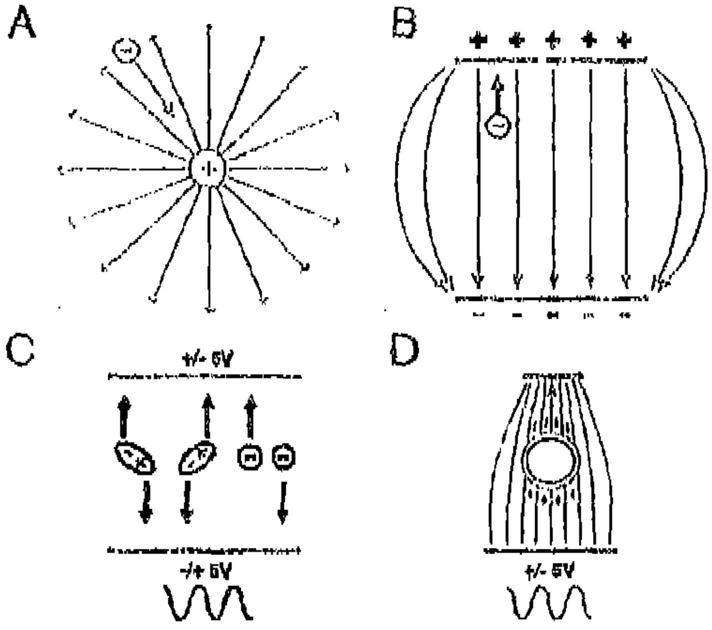

Fig. 1. Electric field theory. (A) Opposite charges attract. (B) A constant, uniform, electric field. (C) Charges and dipoles in a time-varying, uniform electric field. (D) A dipole in a time-varying, nonuniform electric field (dielectrophoresis).

therapy, its antimitotic effect in cultures was enhanced by sequentially applying more than one field direction to the treated cells.[5] The combination of TTF therapy with different chemotherapeutic agents has been shown to have at least additive if not synergistic effects.[7,8] Specifically, the combination of TTF therapy with temozolomide in glioma cell lines was shown to be additive. Interestingly, in breast cancer cells, TTF therapy showed overt synergism with taxanes (e.g., paclitaxel), probably a result of the temporal proximity of taxanes' effect in metaphase and TTF therapy's mitotic interference on cell entry into anaphase.[9]

TTF therapy has been tested in numerous in vivo cancer models (Table 2).[3,5,8,10] Noninvasive application of TTF therapy to animals was performed using electrically insulated transducer arrays placed on the head or torso surrounding the region of the tumor. Inhibition of tumor growth was seen in each of these models when the correct frequency of TTF therapy was applied. Specifically, 200 kHz TTF therapy applied in two sequential and perpendicular field directions lead to significant ($p < 0.01$) inhibition of a syngeneic, orthotopic F-98 glioma in rats after 7 days of treatment.[5] An additional syngeneic, orthotopic model of non-small cell lung cancer in mice showed that 150 kHz TTF therapy significantly ($p < 0.01$) inhibited tumor growth within 7 days of treatment.[8,11] Furthermore, the additive effect of TTF therapy with chemotherapy seen in vitro was recapitulated in different in vivo models.[5,8] Finally, in a metastatic tumor model using a squamous carcinoma tumor implanted in the kidney capsule of rabbits, TTF therapy applied to the abdomen blocked metastatic spread of tumor from the kidney to the lungs.[10,37]

> **KEY POINTS**
>
> - Tumor treating fields (TTF) therapy is an emerging, low-toxicity treatment modality for solid tumors based on the delivery of antimitotic alternating electric fields to the tumor, which interfere with cytokinesis and microtubule assembly that eventually lead to cell death.
> - As a monotherapy, TTF therapy is at least as effective as currently available active chemotherapy and biologic therapies for the treatment of recurrent glioblastoma (GBM).
> - The efficacy of this noninvasive treatment modality is achieved with significantly less toxicity and a better quality of life compared with chemotherapy.
> - Preliminary data suggest TTF therapy acts synergistically with temozolomide and other chemotherapy in both preclinical and clinical trials.
> - Future research should focus on integrating TTF therapy into the treatment of GBM in the adjuvant and maintenance settings, as well as in the treatment of other solid tumor malignancies.

Translating TTF Therapy into Clinical Use

Since TTF therapy is a physical antimitotic modality with no half-life, its application should be continuous. Kinetic modeling was used to predict the minimal treatment duration needed with TTF therapy.[16] Based on those data, a minimal treatment course of 4 weeks was defined and implemented in clinical studies. In vivo animal experiments and pilot clinical data subsequently verified the 4-week minimal treatment duration.[12] Such continuous delivery was made possible by the development of a portable, battery-operated, medical device that patients can use at home (NovoTTF-100A, Novocure, Haifa, Israel). Finally, extensive toxicity studies of TTF therapy were performed in healthy

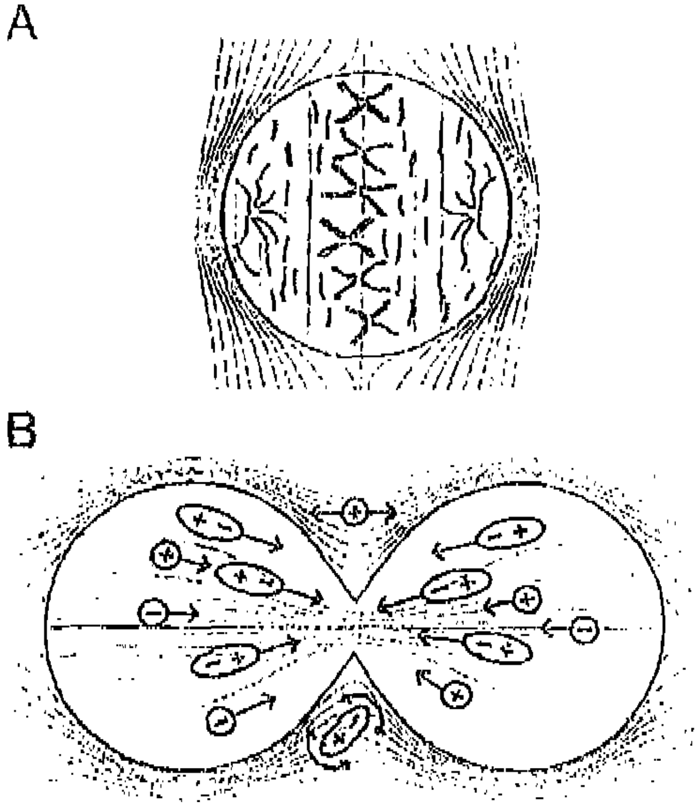

Fig. 2. Effects of tumor treating fields therapy on intracellular structures during mitosis. (A) During metaphase, tubulin dimers align with the external electric field, interfering with the formation of the mitotic spindle. (B) During cytokinesis, the nonuniform electric field formed within the dividing cell drives charged and polar macromolecules and organelles toward the cleavage furrow.

mice, rats, and rabbits.[8,9] Clinical, laboratory, and pathologic analyses showed that TTF therapy is well tolerated and does not lead to systemic toxicity in animals. As expected by the frequency range of TTF therapy (100–300 kHz), these electric fields do not have any effect on excitable tissues (neural, muscular, or cardiac), nor do they cause significant heating.[10-12]

Clinical Testing of TTF Therapy as a Monotherapy

The NovoTTF device was first applied to patients in a small feasibility trial in Switzerland in 2000.[10] In 2004, TTF therapy was tested in a pilot clinical trial in patients with recurrent GBM (Table 2).[8] This single-center, single-arm trial included patients with favorable prognostic character

Table 1. In Vitro Evidence Overview

Histology	Cell line	Optimal/Effective TTF Frequency (kHz)	Additive/Synergistic with Chemotherapy	Reference
High-grade glioma	F-98; C-6; RG-2 U-118; U-87	200	Temozolomide (dacarbazine)	Can Res, 2004[3] Proc Natl Acad Sci U S A, 2007[5]
Breast adenocarcinoma	Normal: MDA-MB-231	120	Cyclophosphamide	Can Res, 2004[3]
	MCF7		Doxorubicin	Neuro Oncol, 2011[4]
	Multiple drug resistant: MDA-MB-231Dox	120	Paclitaxel	BMC Cancer, 2010[7]
	AA8/Emt[R1]		Doxorubicin	
	MCF7/Mx		Paclitaxel	
Non-small cell lung cancer (adenocarcinoma)	H1299	150	Paclitaxel	ERS, 2010[8]
	LLC		Pemetrexed	AACR, 2007[9] Can Res, 2004[3]
Colorectal adenocarcinoma	CT-26	100*	NA	Can Res, 2004[3]
Malignant melanoma	B16F1 Patricia	100	NA	Can Res, 2004[3]
Prostate	PC-3	100*	NA	Can Res, 2004[3]
Cervical cancer	HeLa	200*	NA	Neuro Oncol, 2011[4]

Abbreviations: TTF, tumor treating fields; NA, not available (was not reported by the authors).
*Effect seen at this frequency; additional frequencies were not tested

Table 2. In Vivo Evidence Overview

Tumor Type	Anatomic Location	Animal Model	Frequency (kHz)	Effect of TTF	References
GBM	Right hemisphere	Rat	200	Tumor growth inhibition with 2 and 3 field directions	*Proc Natl Acad Sci U S A*, 2007[4]
Non-small cell lung cancer	Lung parenchyma	Mouse	150	1. Tumor growth inhibition with 2 field directions 2. Additive tumor inhibition with pemetrexed	*ERS*, 2010[8]
Malignant melanoma	Intradermal	Mouse	100	Tumor growth inhibition with 1 and 2 field directions	*Can Res*, 2004[3] *Proc Natl Acad Sci U S A*, 2007[4]
Malignant melanoma	Intravenous	Mouse	100	Inhibition of metastatic seeding in the lungs	*Clin Exp Metastasis*, 2009[10]
VX-2 (anaplastic)	Kidney capsule	Rabbit	150–200	1. Tumor growth inhibition seen with 2 field directions 2. Increase in median survival 3. Inhibition of metastatic seeding in the lungs 4. Additive tumor inhibition with paclitaxel	*Clin Exp Metastasis*, 2009[10] *AACR*, 2009[27] *Neuro Oncol*, 2010[12]

Abbreviation: GBM, glioblastoma.

istics. Treatment with the device was well tolerated, and no treatment-related serious adverse events were reported. Most patients developed grade 1 to 2 contact dermatitis beneath the transducer arrays on the scalp. Efficacy endpoints were very encouraging with a 20% objective response rate, progression-free survival (PFS) at 6 months of 50%, median time to progression (TTP) of 26 weeks, and median overall survival (OS) of 62.2 weeks (14.4 months). Compared to the historic results of salvage chemotherapy, these results showed clear activity of TTF therapy when used as a monotherapy in recurrent GBM.[17]

Based on the results of this pilot trial, a pivotal phase III, multicenter, randomized (1:1) clinical study was initiated in patients with recurrent GBM (Table 3). The randomized study, which recruited 237 patients between 2006 and 2009, compared the efficacy and safety of monotherapy with the NovoTTF device to that of the best available active chemotherapy according to physician's choice. Thirty-six patients received bevacizumab, 36 received nitrosureas, 12 received temozolomide, and 33 received other agents. This was the largest randomized study in recurrent GBM to be completed to date. The results of the study were presented at the 2010 ASCO Annual Meeting and were updated at the 2011 Society for Neuro-Oncology (SNO) Annual Meeting.[18,19] Baseline characteristics of patients were balanced between the two treatment groups. In both groups, patients had poor prognostic predictors compared with previous clinical trials of recurrent GBM (90% of patients were at their second or subsequent recurrence; 20% had failed bevacizumab before entering the trial; and the average tumor diameter was above 6 cm). In the conservative intent-to-treat (ITT) analysis, the study showed that patients with recurrent GBM treated with NovoTTF alone had comparable OS to that of patients who received chemotherapy and/or bevacizumab (6.6 months vs. 6.0 months, respectively; p = 0.26; hazard ratio [HR] = 0.86; Table 3). Although NovoTTF did not show superiority over active chemotherapies, it was clear that it was at least as effective as these treatments. Secondary endpoints in the trial were supportive: blinded radiology review showed that PFS at 6 months was 21.4% in the NovoTTF group compared with 15.2% in the chemotherapy group (p = 0.24). There were more radiological responses seen in the NovoTTF group compared with the chemotherapy group (12% vs. 6%, respectively; p = 0.07), including

Table 3. Clinical Evidence Overview

Indication (Analysis Group)	Trial Phase (# of Subjects) Analysis	Overall Survival (Months) TTF	Overall Survival (Months) Chemo	Hazard Ratio (p)	Progression-Free Survival (PFS) at 6 Months or Median PFS (Weeks) TTF	PFS Chemo	P value	References
Recurrent GBM (at first relapse)	Phase I-II (n = 10) *ITT Analysis*	14.5 m	6.0 m*	Non-randomized	50%	15%*	NA	*Proc Natl Acad Sci U S A*, 2007[3]
Recurrent GBM (at second and fourth relapse)	Phase III (n = 237) *ITT analysis*	6.6 m	6.0 m	HR = 0.86 (p = 0.26)	21.4%	15.2%	p = 0.24	*J Clin Oncol*, 2010[18] *Neuro Oncol*, 2011[19]
Recurrent GBM (treated patients only)	Phase III (n = 210) *PP Analysis*	7.8 m	6.0 m	HR = 0.67 (p = 0.012)	26.2%	15.2%	p = 0.03	*J Clin Oncol*, 2010[18] *Neuro Oncol*, 2011[19]
Recurrent GBM (KPS ≥ 80, age < 61)	Phase III (n = 110) *Subgroup analysis*	8.8 m	6.6 m	HR = NA (p < 0.01)	25.6%	7.7%	NA	*Neuro Oncol*, 2010[19]
Recurrent GBM (after bevacizumab failure)	Phase III (n = 43) *Subgroup analysis*	4.4 m	3.1 m	(p = 0.02)	NA	NA	NA	*Neuro Oncol*, 2010[20]
Recurrent GBM (TTF versus bevacizumab)	Phase III (n = 156) *Subgroup analysis*	6.6 m	5.0 m	HR = 0.65 (p = 0.048)	21%	21%	p > 0.05	*Neuro Oncol*, 2011[21]
Newly diagnosed GBM (together with temozolomide)	I-II (n = 10) *ITT Analysis*	39+ m	14.7 m*	(p = 0.002)	90% 156 w	50%* 26 w	NA	*BMC Med Phys*, 2009[9]
Relapsed advanced NSCLC (together with pemetrexed)	I-II (n = 42) *ITT Analysis*	13.8 m	8.2 m*	NA	26 w	12 w*		*ESMO*, 2010[25] *ERS*, 2010[8] *Expert Opin Investig Drugs*, 2010[11]

Abbreviations: GBM, glioblastoma; ITT, intention to treat; NA, not available (was not reported by the authors); HR, hazard ratio; PP, per protocol; KPS, Karnofsky performance status; TTF, tumor treating fields; NSCLC, non-small cell lung cancer.
* Single-arm trials with literature control.

three sustained complete responses in the NovoTTF group compared with none in the chemotherapy group. These results were accompanied by significantly ($p < 0.05$) less treatment-related adverse events with NovoTTF compared with chemotherapy. Patients in the NovoTTF group reported a higher quality of life compared with patients treated with chemotherapy. This analysis was based on the European Organisation for Research and Treatment of Cancer QLQ-C30 and mirrored the lack of chemotherapy-related toxicities in the NovoTTF group. Interestingly, patients in the NovoTTF group reported better cognitive and emotional functioning and much less pain than patients in the chemotherapy group, although these domains of the questionnaires are not related to known side effects of chemotherapy.

To date, several exploratory analyses of the study data have been performed. The first analysis compared patients who received the same "amount" of therapy in both groups. This prospectively defined per-protocol analysis excluded patients from both groups who received less than one predefined treatment course. The analysis demonstrated superior survival in the NovoTTF group compared with the chemotherapy group (7.8 months vs. 6.0 months; $p = 0.012$, HR = 0.67).[18,19] The rationale behind this analysis is that TTF is a physical modality with no half-life, so that the moment the therapy is stopped, its antimitotic effect stops as well. In contrast, chemotherapies have measurable plasma and tissue half-life, which results in continued efficacy and toxicity long after a dose has been given. Therefore, to achieve pharmacokinetic balance in the "amount" of treatment in both groups, this analysis used a simplified criterion that one course of chemotherapy (e.g., 1 day of carmustine or 5 days of temozolomide) is equivalent to four weeks of continuous TTF therapy.

Two more analyses of the study data were presented at the 2010 and 2011 SNO Annual Meetings.[20,21] The first study analyzed known clinical prognostic factors of age and Karnofsky performance status (KPS). This analysis demonstrated that in patients age 60 and younger with a KPS greater than 70, treatment with NovoTTF resulted in superior OS compared with chemotherapy (8.8 months vs. 6.0 months; $p < 0.01$). This survival advantage could be attributed to better compliance with TTF therapy in this group of patients. In support of this finding, a statistically significant correlation was seen in the NovoTTF group between treatment compliance (as measured by the device computerized log file) and OS ($p = 0.0476$).

The second analysis is a post hoc, exploratory analysis of the treatment of 120 patients with NovoTTF compared with 36 patients with bevacizumab. Although without a prespecified analysis in the trial, patients in the study treated with NovoTTF lived significantly longer than those treated with bevacizumab (6.6 months vs. 5.0 months, respectively; $p = 0.048$, HR = 0.65).[21] This analysis included all TTF patients who received either bevacizumab or NovoTTF. Patient characteristics were almost identical and, in fact, favored the bevacizumab group prognostically. Clearly, this analysis cannot be taken as final evidence of superiority of NovoTTF over bevacizumab; however, it should be treated as hypothesis-generating data for future clinical studies. Finally, in the 43 patients who entered the study after bevacizumab therapy failure (approximately 20% of patients in both groups), OS was significantly longer with TTF therapy than with chemotherapy (4.4 months vs. 3.1 months, respectively; $p = 0.02$). The data for the chemotherapy-treated group is in line with previous publications, which showed that following bevacizumab failure, the survival of patients with recurrent GBM is limited.[22]

Based on the results of this pivotal phase III study, the FDA approved the NovoTTF-100A device on April 8, 2011, through the premarket approval (PMA) regulatory pathway. The PMA pathway is reserved for class III (high-risk) medical devices and requires preclinical, clinical, and manufacturing evidence, including review of both efficacy and safety data by a panel of independent experts. The FDA concluded that the study results showed NovoTTF to be comparable in efficacy to active chemotherapy, without many of the side effects associated with chemotherapies and with a better quality of life.[23]

Clinical Trials Evaluating TTF Therapy in Combination with Chemotherapy

Two studies of combined TTF therapy and chemotherapy have been published to date. The first was a single-arm, single-center trial performed in 2006 in patients with newly diagnosed GBM.[9] Patients received the Stupp protocol with TTF therapy added to maintenance temozolomide.[24] This trial showed promising PFS and OS data (PFS > 14 months; OS > 39 months; Table 3) and served as the basis for an ongoing, multicenter, pivotal phase III, randomized clinical study comparing TTF therapy and temozolomide with temozolomide alone in the maintenance stage of the Stupp protocol.

The second study tested TTF therapy together with pemetrexed in 42 patients with pretreated, advanced non-small cell lung cancer.[5,11,25] Efficacy and safety with this combined treatment paradigm were promising. Time to local disease progression in the lungs and liver (where TTF was applied) was 28 weeks, and OS was 13.8 months. In contrast, TTP and OS for pemetrexed alone were previously reported to be 12 weeks and 8.3 months, respectively.[26]

TTF therapy is still in its early days. However, it has an established mechanism of action, and a growing body of preclinical evidence has shown its wide applicability in solid tumor malignancies either alone or in combination with standard chemotherapies. Objective antitumor activity and an unprecedented safety profile of this treatment modality have been seen in patients with recurrent GBM. Although TTF monotherapy has been shown to be at least as effective as the best available chemotherapies today for recurrent GBM, in-depth analysis of the phase III study data identified at least two subgroups where TTF therapy was superior to chemotherapy and could be offered to patients as an alternative to chemotherapy: younger patients with a better functional status and patients in whom bevacizumab treatment has failed in the past.

Conclusion

The approval of TTF therapy for recurrent GBM ushers in a fourth modality of cancer treatment. More importantly, TTF treatment has a superior safety profile, and its minor side effects do not appear to overlap with those of cytotoxic chemotherapies, targeted agents, or antiangiogenesis drugs. Therefore, the rational combination of TTF therapy with specific pharmacologic agents may enhance tumor cell death

because of potential additive or synergistic effects. First, as demonstrated in preclinical and clinical models, chemotherapy administered together with TTF therapy may result in additive or synergistic tumor control without increasing systemic toxicities. Second, TTF treatment could be combined with targeted agents that block survival signaling within the tumor cell. This block may be sufficiently strong to enhance the cytotoxic effect of TTF therapy or vice versa. Third, the combination of TTF and antiangiogenesis agents may be another promising path that combines different antitumor treatments to improve tumor control. Lastly, the proper scheduling of TTF therapy with other agents is unknown. Additional research may shed light on the optimal scheduling that may achieve a synergistic effect on tumor growth leading to long-term tumor control and enhanced patient survival.

Authors' Disclosures of Potential Conflicts of Interest

Author	Employment or Leadership Positions	Consultant or Advisory Role	Stock Ownership	Honoraria	Research Funding	Expert Testimony	Other Remuneration
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PNAS

Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors

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We have recently shown that low intensity, intermediate frequency, electric fields inhibit by an anti-microtubule mechanism of action, cancerous cell growth *in vitro*. Using implanted electrodes, these fields were also shown to inhibit the growth of dermal tumors in mice. The present study extends these findings to additional cell lines [human breast carcinoma; MDA-MB-231, and human non-small-cell lung carcinoma (H1299)] and to animal tumor models (intradermal B16F1 melanoma and intracranial F-98 glioma) using external insulated electrodes. These findings led to the initiation of a pilot clinical trial of the effects of TTFields in 10 patients with recurrent glioblastoma (GBM). Median time to disease progression in these patients was 26.1 weeks and median overall survival was 62.2 weeks. These time to disease progression and OS values are more than double the reported medians of historical control patients. No device-related serious adverse events were seen after >70 months of cumulative treatment in all of the patients. The only device-related side effect seen was a mild to moderate contact dermatitis beneath the field delivering electrodes. We conclude that TTFields are a safe and effective new treatment modality which effectively slows down tumor growth *in vitro*, *in vivo* and, as demonstrated here, in human cancer patients.

cancer | glioblastoma | tumor treating fields

Because living cells consist of ions, polar or charged molecules, membranes, and organelles, they are responsive to and often generate electric fields and currents. The electric activity of cells plays a key roll in many essential biological processes. The electric fields associated with all of the above phenomena are in the range of 0–10 V/cm, except within cell membranes (1) where they may reach 10^5 V/cm. Whereas electric fields induce ion flow, polar molecules only orient themselves along the lines of a uniform field (2). However, nonuniform electric fields exert forces on polar molecules forcing them to move toward higher field intensity, a well known process known as dielectrophoresis (3, 4). Electric fields and resulting currents, when sufficiently large, stimulate nerves, muscles, cardiac muscle, etc. Only much larger fields generate heat that may damage cells (5).

In an electric field of alternating direction (ac field) all charges and polar molecules are subjected to forces of alternating direction so that ionic flows and dipole rotation oscillate (Fig. 1). In view of the relatively slow kinetics of the bioelectrical responses, as the ac fields' frequency is elevated, their biological effect (except for heating) is reduced such that, >10 kHz, it becomes negligible. Therefore, it is generally believed that ac fields of 100 kHz or above have no meaningful biological effects (5), although a number of nonsignificant effects have been described (6–8).

In contradiction to this belief, we have recently demonstrated (9) that 100 KHz to 1 MHz ac fields have significant specific effects on dividing cells. The basis of these effects during cytokinesis was shown to be the unidirectional forces induced by the inhomogeneous fields at the bridge separating the daughter cells (Fig. 1*B*) that interfere with spindle tubulin orientation and induce dielectrophoresis.

It is the aim of this work to further study the effects of ac fields on quiescent and proliferating cells in culture, animal cancer models, and cancerous tumors in humans. Following a basic work on cell cultures (9), we demonstrate here that such fields, termed tumor treating fields (TTFields), are effective when applied by insulated external electrodes to animal cancer models and patients with recurrent glioblastoma (GBM). In a pilot clinical trial conducted on this extremely malignant tumor of glial cell origin (10, 11), TTFields treatment was found to be both safe and effective in slowing tumor progression. These promising results raise the possibility that TTFields could become a new treatment modality for cancer.

Cells in Culture

The effects of a 24-h exposure of four of the most common types of cancer (malignant melanoma, glioma (part of the data for malignant melanoma and glioma cells was taken from ref. 9), breast carcinoma, and non-small-cell lung carcinoma to TTFields] are illustrated in Fig. 2. It is seen that the number of unexposed (control) cells roughly doubles every 24 h, whereas the proliferation rate of the exposed cells is slowed down during exposure and gradually recovers after treatment is terminated (Fig. 2*A*). The frequency dependency of the effects is depicted in Fig. 2*B*. It is seen that the optimal frequency is 100 kHz for mouse melanoma (B16F1), 150 kHz for human breast carcinoma (MDA-MB-231), and 200 kHz for rat glioma (F-98). In addition, similar experiments were performed in two human glioma cell lines (U-118 and U-87). In both, the optimal TTFields frequency was identical to rat glioma cell lines (i.e., 200 kHz).

The "dose-response curve," i.e., the relationship between the TTFields effects and field intensity, is given in Fig. 2*C*. It is seen that effect on cell division and cell death (by apoptosis) is intensity dependent, the sensitivity being highest for mouse

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Abbreviations: FEM, finite element mesh; GBM, glioblastoma; OS, overall survival; PFS6, progression-free survival at 6 months; TTFields, tumor treating fields; TTP, time to disease progression.

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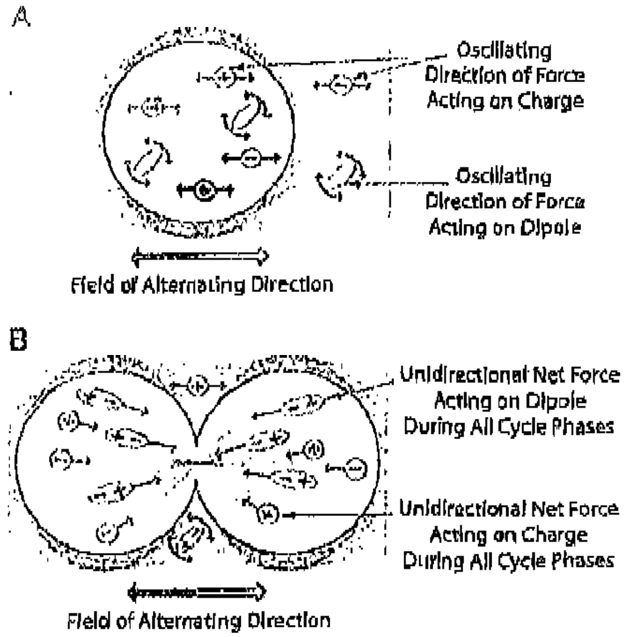

Fig. 1. ac field distribution in and around quiescent (*A*) and dividing (*B*) cells. Inside quiescent cells, the field is uniform, and the oscillating electric forces result only in "vibration" of ions and dipoles (the forces associated with each half cycle are denoted white and gray arrows). In contrast, the nonuniform field within dividing cells (*B*) induces forces pushing all dipoles toward the furrow. Note that at frequencies of 0.1–1.0 MHz, the cell membrane impedance is relatively high, so only a small fraction of the currents penetrate the cells as seen from the density of lines.

melanoma cells, decreasing for rat glioma and for human non-small-cell lung carcinoma and lowest for human breast carcinoma.

From the mechanism of action of TTFields, as illustrated in Fig. 1, it can be deduced that their efficacy must be a function of the angle between the field and axis of division; when the two are parallel its maximal and when one is perpendicular to the other, it must be minimal. Because in culture the axis of division is randomly oriented, only a fraction of the dividing cells are subjected to optimal treatment. To overcome this problem, multiple field directions were applied sequentially every 0.25 -1 sec. Two perpendicular fields were found to be ~20% more effective than the single-direction one for B16F1 and F-98 cells. This result is consistent with the previously reported effects on malignant melanoma cells (9).

Animal Tumor Models

Intracranial Glioblastoma. Our report (9) described the effects of TTFields applied by means of implanted electrodes to intradermal malignant melanoma in mice. This report compares 40 Fischer rats inoculated intracranially with glioma cells, treated by means of external electrodes with a temperature, and geometry matched electrode control group. The treatment duration was 6 days, using the optimal frequency of 200 kHz (see Fig. 2) at 2 V/cm. Fig. 3 depicts the computed field distribution in the rat brain (Fig. 3*A*), exemplary posttreatment MRI images of a control (Fig. 3*B*) and a treated tumor (Fig. 3*C*). The maximal diameter of the treated tumor is about half that of the control one.

The average inhibitory effect of unidirectional TTFields (in a temporal-temporal direction) was small and did not reach statistical significance (treated tumor volume 19.8% smaller than sham control tumors; $n = 26$; $P = 0.19$, Student's *t* test). However, increasing the number of TTFields directions caused statistically significant inhibition of tumor growth, reaching 42.6% and 53.4% for two ($n = 42$; $P < 0.01$, Student's *t* test) and three ($n = 10$; $P < 0.01$, Student's *t* test) directions positioned at 45–90° to each other, respectively.

Frequency Dependence of the Inhibitory Effect of TTFields. The TTFields inhibitory efficacy vs. frequency was studied on mice inoculated with B16F1 melanoma. The mice ($n = 26$) were treated for 5 days by single-direction TTFields of different frequencies. The maximal growth inhibition was found at 100 kHz, with the treated tumor size 62.7 ± 8.9% that of control tumors. Although this frequency dependence *in vivo* did not reach statistical significance (single-factor ANOVA, $P = 0.11$), it shows the same frequency dependency as the dependence of cultured B16F1 cells reported in ref. 9, which supports the

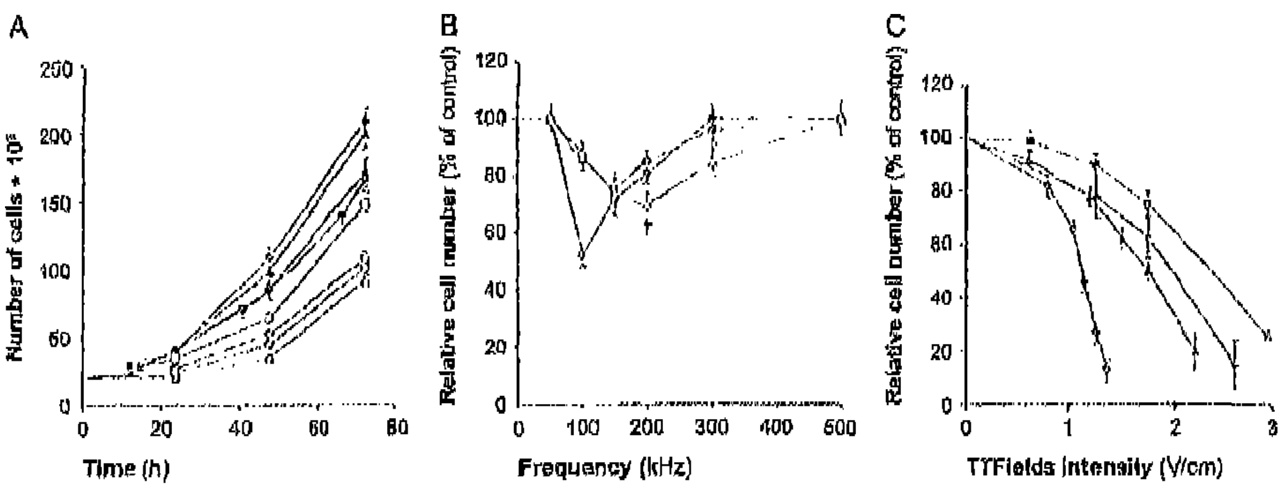

Fig. 2. Time, frequency, and intensity dependence of the effect of TTFields on cancer cell proliferation. (*A*) The number of cells in untreated cultures (filled symbols) as compared with cultures treated with TTFields (open symbols) for 24 h (1.75 V/cm for MDA-MB-231, F-98, and H1299 cells and 1.1 V/cm for B16F1 cells). (*B*) The relative change in number of cells after 24 h of treatment of different frequencies (same TTFields intensity). (*C*) The effect of 24 h of exposure to TTFields of increasing intensities (at optimal frequencies). ● and ○, B16F1; ■ and □, MDA-MB-231; ▲ and △, F-98; ♦ and ◇, H1299.

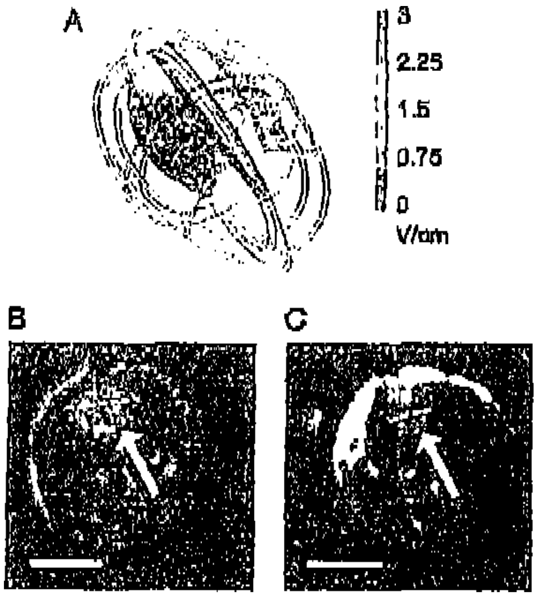

Fig. 3. TTFields inhibition of the growth of intracranial glioma. (A) FEM simulations (using a three-dimensional mesh) of the distribution of TTFields intensity within a simplified rat brain model. (B and C) Exemplary T1 weighted coronal MRI sections (after IV injection of Gd-DTPA) of the heads of a control and a TTFields treated (200 kHz, two-directional TTFields) rat, respectively. In both examples, the section shown is that with the largest diameter tumor. Head simulations are 3.1 × 1.9 cm ellipsoid; skin thickness, 0.4 mm (σ = 0.00045 S/m; ε = 1,120); skull thickness, 1.1 mm (σ = 0.015 S/m; ε = 10); thickness of the CSF surrounding the brain, 0.5 mm (σ = 2 S/m; ε = 100); and brain itself has the properties of a uniforms white matter (σ = 0.15 S/m; ε = 3,200). The electrodes placed over a 0.5-mm layer of hydrogel. Note the almost uniform field intensity in most brain volume. (Scale bars, 1 cm.)

conclusion that this is the optimum frequency. In contrast, rats bearing intracerebral glioma were unaffected by 100 kHz TTFields, whereas 200 kHz TTFields caused significant inhibition of tumor growth.

Safety Profile of TTFields in Healthy Animals. TTFields (100 kHz) at 6 V/cm were applied to the chest of three New Zealand rabbits. No changes were seen in the rate or regularity of cardiac rhythm throughout and following the exposure. To test the safety of chronic TTFields application TTFields were applied to either the head (n = 30, 1 V/cm for 4 weeks) or the chest (n = 10, 3 V/cm for 2 weeks) of New Zealand Rabbits. All animals were assessed weekly for weight, temperature, ECG, CBC, wide chemistry panel and coagulation. After a 1-month follow-up period, all animals were killed and had samples of major organs examined by a pathologist. No treatment-related toxicities were recorded in any of the animals.

GBM Patients

TTFields Treatment of Patients with Recurrent GBM Brain Tumor. Ten patients with recurrent GBM were included in the trial (see *Materials and Methods* and supporting information (SI) Table 1).

As seen in Fig. 4*A*, the median time to disease progression (TTP) of the patients is 26.1 weeks (range 3–124 weeks) and the progression-free survival at 6 months (PFS6) is 50% (23–77%; 95% confidence interval). Two of the patients were still progression free at study closure.

The median overall survival (OS) of TTFields treated patients is currently 62.2 weeks (range 20.3–124.0 weeks). These TTP and OS values are more than double the reported medians of historical control patients. Three of the patients are still alive at this time. The Kaplan–Meier survival curve (12) of the treatment results is shown in Fig. 4*B*.

The TTFields treatment resulted in one complete response (Fig. 5*A*) which is still tumor free per MRI ten months after stopping treatment and one partial response (Fig. 5*B*) that is still responding 7 months after stopping treatment. Both are still progression free >2 years from treatment initiation. In addition one patient had minimal response and four had stable disease for over 4 months before progressing.

Safety Profile of TTFields Applied to GBM Patients. The 10 recurrent GBM Patients received treatment for a total of 280 weeks without a single treatment-related serious adverse event and no significant changes were seen in serum chemistry or blood count in any of the patients. The only changes seen consistently were elevated liver enzymes, attributed to anti-epileptic drug usage. Two patients had partial seizures that were unrelated to treatment. Nine of ten patients suffered from a mild to moderate contact dermatitis beneath the electrode gel. This treatment-related adverse event responded well to application of steroid creams and periodic electrode relocation.

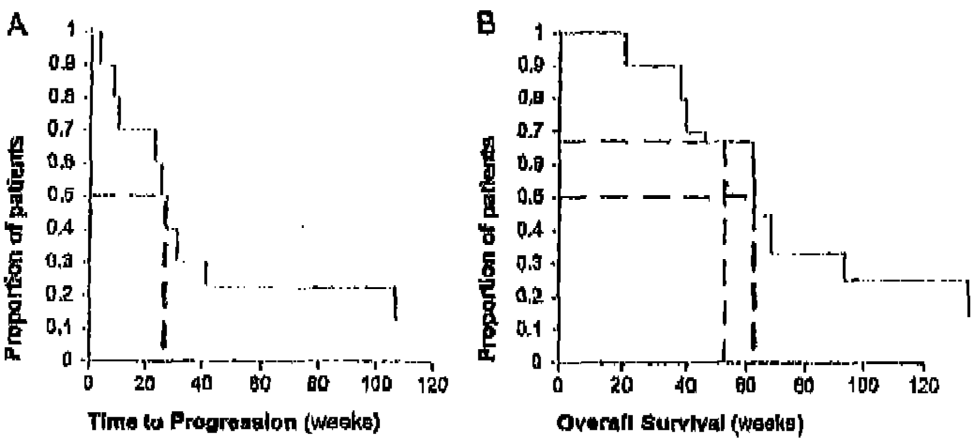

Fig. 4. Efficacy of TTFields treatment in recurrent GBM. (A) TTP of treated patients (n = 10); median TTP is 26.1 weeks (dashed black line). (B) Kaplan–Meier OS curve for NovoTTF-100A treated patients (n = 10). The median OS in these patients is 62.2 weeks (black dashed line), and the 1-year survival rate is 67.5% (blue dashed line).

A

B

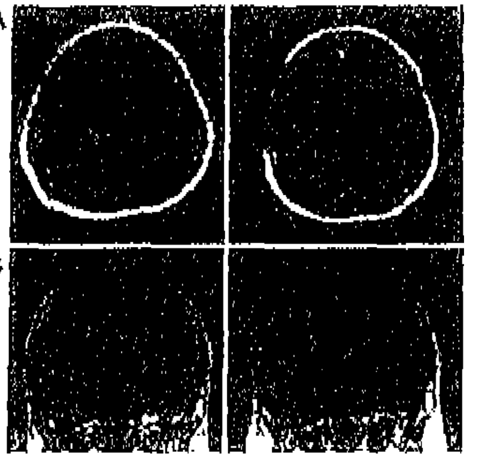

Fig. 5. *Exemplary T1-weighted, post contrast, MRI scans of recurrent GBM patients before (Left) and after (Right) TTFields treatment. (A) Complete response after 8 months of treatment. (B) Stable disease (10% reduction in contrast enhancing area) after 9 months of treatment.*

Discussion

Alternating electric fields have been shown to have a wide range of effects on living tissues. At very low frequencies (<1 KHz), electric fields stimulate excitable tissues through membrane depolarization (13) and have been claimed to stimulate bone growth and accelerate fracture healing (14). However, as the frequency of the electric field increases the stimulatory effect diminishes, whereas above MHz a completely different biological effect, tissue heating, becomes dominant (15, 16).

Alternating electric fields of intermediate frequencies (10 kHz to 1 MHz) were considered not to have any meaningful nonthermal biological effects (5). An exception, are the TTFields described in ref. 9. This presumed lack of effect of such fields is consistent with the fact that when electric fields, that exert forces only on charges and dipoles reverse direction at a high frequency, their net effect tends to null out. Thus, the effects were minor and have neither been shown to be beneficial or detrimental to humans (5, 6, 17).

In this study we try to use TTFields as a new cancer treatment modality. We first extended the In-Vitro study of TTFields effect on glioma and melanoma cells (9) to several of the most prevalent cancers; breast carcinoma and non-small-cell lung carcinoma. It was found that the proliferation of these cells is arrested and the cells are destroyed (Fig. 2). The optimal frequencies differed between cancer cell types. To understand this finding we calculated the force on a 1 μm polarizable spherical particle in a dividing cell as function of cell radius, membrane thickness and cytoplasm conductivity. It was found that optimal TTFields frequency is inversely related to cell size (see *SI Appendix A*) in a way consistent the diameter variability of the different cell types studied.

In the previous study (9) animal treatment was done by using implanted electrodes. In the present study, we used the much more practical externally applied electrodes. Furthermore, as the available data suggests that treatment may need to be prolonged, the use of conducting electrodes may result in serious problems: local damage to the skin because of electrolysis and the generation of free radicals at the electrode-tissue interface, skin permeabilization by the transdermal currents (18, 19), and calcium accumulation within cells (20) that can result in cell death (21). Clearly, the first 2 adverse effects do not occur at the surface of insulated electrodes. Using fluorescence calcium imaging techniques, we could demonstrate that electric field induced calcium accumulation is eliminated by the use of insulated electrodes (see *SI Appendix B*). However, the large potential drop across the insulation high impedance poses a serious problem; to generate the fields of the required intensity potentials of >1,000 V must be used. As such high voltages may compromise patient safety, low impedance electrodes were developed. The impedance of insulation is lowered by using an insulating material, lead magnesium niobate-lead titanate (PMN-PT) (EDO, New York, NY), that has a dielectric constant of $\varepsilon > 5,000$. Under these conditions the electrodes have a capacitance of ≈10nF/cm², i.e., an impedance of 100–200 Ω at the TTFields frequency range. Thus, only 50% of the applied voltage is lost on the insulation in the mice experiments. The corresponding potential drop on the 22.5 cm² electrodes placed on the patient's head, in the trial presented here, is only ≈10% of the applied voltage.

A major limitation of all current cancer treatments is their unfavorable therapeutic index. Two types of toxicities may be expected from an electric field based treatment. First, the fields could theoretically affect excitable tissues causing cardiac arrhythmias or seizures. However, such effects are not expected to occur, because for sinusoidal alternating fields of >10 kHz, excitation of nerves and muscles decreases dramatically, because of the parallel resistor-capacitor nature of the cell membrane (22). Indeed, in both acute and chronic application of TTFields to animals and patients, there was no trace of abnormal cardiac or neurological activity. Secondly, TTFields might be expected to damage rapidly dividing normal cells within the body, i.e., bone marrow and small intestine mucosa. However, no treatment-related toxicities were found in any of the treated patients or upon animal exposure to field intensities threefold higher than the effective anti-tumoral dose. With regards to hematopoesis the reason for this is that these cells, which reside mainly in the bone marrow, are protected from the TTFields by the high impedance of both the bone and bone marrow (23). This was demonstrated by calculating the TTFields distribution in an extremity, such as a leg, by using the finite element mesh (FEM) method. It was found that the field intensity is 100-fold lower within the bone marrow compared with the surrounding tissues. The lack of damage to intestinal mucosa probably reflects that the small intestine mucosal cells have a slower replication cycle than neoplastic cells (24) and that the intestine changes its orientation, relative to the applied field, often lowering the efficiency of the mitotic disruption.

The tumor inhibitory effect of TTFields has been attributed previously to two separate mechanisms (9): interference with the formation of the mitotic spindle microtubules and physical destruction of cells during cleavage, both of which are strongly dependent on the orientation of mitosis axis versus the field vectors. Because the relative orientation of the mitosis axis during cytokinesis is random, it would be expected that only a fraction of dividing cells would be affected by TTFields of any specific direction. To overcome this problem, we applied sequentially several field directions and have shown that increasing the number of directions from 1 to 3, resulted in a significant increase in the anti-proliferative efficacy of TTFields *in vitro* and *in vivo*.

Following encouraging evidence from experimental animals, a clinical trial of the effect of TTFields on patients with recurrent GBM was initiated. Because *in vitro* data indicate that TTFields are most effective when applied for >16 h continuously (data not shown), patients were treated daily for an average of 18 h per day until progression. The results reported here are the first evidence of the safety and efficacy of TTFields used to treat cancer in patients. Preliminary accounts of this data were published in

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abstract form.[¶§***] Because this was a pilot trial there was no randomized control group and the results were evaluated by comparing to historical control data. Most historically controlled pilot studies in recurrent GBM are compared with a large metaanalysis performed by Wong *et al.* in 1999 (10) and to this data we added the four prospective trials (25–28), which included >50 GBM patients, performed since that date. The average historical PFS6 based on the above studies is 15.3 ± 3.8%, and the average historical TTP is 9.5 ± 1.6 weeks. OS averaged 29.3 ± 6 weeks (see SI Table 2). When compared with these outcomes, the efficacy data collected in the current pilot trial is extremely promising (TTP, 26.1 weeks; PFS6, 50%; and OS, 62.2 weeks). These results were not accompanied by hematological or gastrointestinal toxicities, epileptic seizures, cardiac arrhythmias, etc., despite >70 months of cumulative treatment. The only side effect detected was contact dermatitis beneath the electrodes. This reaction is most likely the result of a combination of factors, including chronic moisture, heat, and occlusion of the skin; chemical irritation by constituents of the hydrogel and medical tape (29); and possibly inhibition of cellular replication in the skin by the TTFields. Thus, in conclusion, this treatment modality was well tolerated and caused almost no toxicity at all.

In summary, we demonstrated initially that TTFields are effective in arresting the proliferation and inducing death in a wide range of tumor cells in culture as well as solid tumors in animals. On this basis a clinical trial was carried out treating human patients suffering from recurrent GBM, a malignant brain tumor. It was demonstrated that the TTFields inhibit the growth of this highly treatment-resistant tumor by using special insulated electrodes, with little or no side effects. Can we expect to have similar efficacy on other human tumors? The fact that in cultures and animal models TTFields were found to be effective on all cells and tumors tested is definitely encouraging. Furthermore, TTFields being a physical, rather than chemical, modality, their efficacy is likely to be highly insensitive to specific interactions with tumor and patient receptors and other characteristic elements. Thus, like irradiation, they have the potential to be effective over a wide range of tumors. However, from the above it is apparent that their practical specificity to cancerous cells is significantly higher than that of irradiation, the therapeutic efficacy of which is often severely limited by toxicity. Therefore, we believe that there is a high probability that TTFields may prove to be an effective and safe therapeutic modality to a large number of human cancers.

Materials and Methods

Cell Cultures. Cell cultures were grown in DMEM plus 10% FCS media in a CO_2 incubator (5% CO_2) at 37°C. Cell suspension (200 μl; total 20 × 10^3 cells) were placed as a drop in the centre of 35-mm Petri dishes, incubated for 24 h and then the cell number was estimated by using standard XTT method (Cell proliferation assay Kit, Biological Industries Ltd., Israel) and expressed as OD_0. Temperature was measured by a thermocouple (Omega, Stamford, CT) placed at the center of the dish. Two pairs of electrodes, insulated by a high dielectric constant ceramic [lead magnesium niobate–lead titanate (PMN-PT)], positioned in the petri dish perpendicular to each other were connected to a sinusoid function generator and amplifier. Two-directional fields were generated sequentially (1) by switching the output of the amplifier between two pairs of electrodes every 0.25–1 sec. The electric field intensity in the culture medium was measured as described in ref. 1.

At the end of 24 h of treatment, the cell number was measured by using the XTT method and expressed as OD_1. The rate of cell proliferation was expressed as the OD_1/OD_0 ratio.

Animal Models. ***Tumor inoculation and in vivo size assessment.*** Animal experiments were conducted after approval by the Technion–Israel Institute of Technology committee for the care of laboratory animals. Intracranial glioma (F-98) was inoculated stereotactically into the subcortical white matter in the right hemisphere of Fischer rats (Harlan laboratories, Israel) by using a modification of the method described in refs. 30 and 31. Briefly, a hole, 1 mm in diameter, was punched through the scalp, 2 mm to the right of the midline and 4 mm rostral to the line connecting the external ear canals. A 0.5 mm burr hole was drilled in the bone at same location and a 26G needle was inserted to a depth of 7 mm beneath the scalp surface. Five microliters of saline containing 2.5 × 10^5 F-98 cells was then injected by using a microsyringe operated by a micromanipulator. The needle was left in position for 60 sec and then retracted slowly at a rate of 2 mm/min. Rats were allowed to recuperate for 24 h before treatment initiation. Tumor volume was assessed based on serial (2-mm interval) T1 weighted axial MRI images (0.5 Tesla MRI; Gyrex orbital coil; Elscint; Haifa, Israel) obtained 10 min following injection of 0.7 ml of Gadolinium (Magnevist; Soreq Radiopharmaceuticals, Yavne, Israel) into the tail vein. Tumor volume was assessed by calculating the area in square millimeters of the contrast enhanced lesion in each section. In view of the small size of the head of the rat, only three electrodes could be positioned on it, generating one to three different field directions.

Computation of the distribution of electric fields generated by external insulated electrodes. The distributions of the alternating electric field generated by external electrodes within the brains of rats were estimated by using FEM simulations. These field distributions are determined by the geometry and electrical properties of the electrodes and tissues. On average, the capacitance of each electrode is 8 nF. This translates into an impedance of 190 and 95 Ω at 100 and 200 kHz, respectively. Because the impedance of the rat head is on the order of 400 Ω, when applying 42 V, 200 kHz TTFields to rats, 14-V drop on the insulation of both electrodes and the remaining 28 V on the rat itself. The fields generated in the areas of interest are in the range of 1–2 V/cm. The calculated field distribution for the rat head is given in Fig. 3A.

Human GBM Trial. ***GBM patient eligibility and characteristics.*** Twelve patients, suffering from the brain tumor GBM were enrolled to the study. Patients eligible for enrollment had recurrence based on Macdonald criteria (32), were >18 years old, had histologically established GBM (World Health Organization grade IV), had a Karnofsky performance scale ≥ 70, and were at least 4 weeks from any brain surgery and at least 8 weeks from radiotherapy. Patients could be at any recurrence and may have received other salvage therapies before enrollment. All patients had received adjuvant Temozolomide for their primary tumor. No concomitant chemotherapy was allowed. Multifocal disease was allowed. Patients with significant comorbidities, infratentorial tumors, implanted pacemakers or documented clinically significant arrhythmias, were excluded from the trial. During review of the histology from postprogression debulking surgery, one patient was excluded from efficacy analysis because of failure to meet histological criteria for grade IV glioma. An additional patient dropped out of the trial immediately following the baseline visit because of withdrawal of consent. Individual patient characteristics are listed in SI Table 1.

¶Kirson, E. D., Dbalý, V., Rochlitz, C., Tovaryš, F., Salzberg, M., Palti, Y., *AACR Meeting Abstracts*, April 5, 2006, Washington, DC, Abstract 5259.

§Dbalý, V., Kirson, E. D., Palti, Y., Gutin, P.H., *Congress of Neurological Surgeons*, October 13, 2005, Boston, MA (abstr.).

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The clinical trial. A single arm, pilot trial of the safety and efficacy of TTField treatment was performed in 10 patients with recurrent GBM. Written informed consent was obtained from each subject. The trial was performed after approval by the Na Homolce Institutional Review Board and the Czech Ministry of Health. Efficacy analysis was performed for 10 recurrent GBM patients by comparing TTP, PFS6, and OS in recurrent GBM patients treated with the NovoTTF-100A device with the TTP, PFS6, and OS of recurrent GBM patients in a literature based historical control group (10, 25–28). No statistical hypothesis testing was planned because of the small sample size. Ninety-five percent confidence intervals of survival proportions were calculated from Kaplan–Meier survival curves, by using standard formulae (33).

Measurement and simulation of TTFields intensity within the human brain. To plan the TTFields intensity necessary to treat patients with intracranial tumors, we performed FEM simulations of the intensity distribution of TTFields within a three-dimensional model of the human head. Field intensity was slightly higher in the cortex than in the center of the brain (by ≈30%), but effective (1–2 V/cm) TTFields could be generated at the center of the brain by applying ≈50 V to surface electrodes placed on the scalp. To validate these findings, TTFields intensity was measured within the brain of a volunteer undergoing surgery because of obstructive hydrocephalus because of a huge meningioma of the pineal region. The study was performed according to an experimental protocol approved by the Rambam Medical Center ethics committee. The measured TTFields intensity was accurate within 10% of the FEM simulated values.

TTFields treatment of GBM patients. TTFields were applied to recurrent GBM patients by using the NovoTTF-100A device (NovoCure Ltd., Haifa, Israel). This portable battery-operated device generates TTFields in GBM patients by means of insulated electrodes placed on their shaved scalps. The area of each insulated electrode array used was 22.5 cm². Fields of 1–2 V/cm were generated by controlling the current density through the electrodes <31 mA/cm² RMS, approximately one-third of the level that is generally recognized to present a risk of skin injury (100 mA/cm²) (34). In addition, the maximal power density beneath the electrodes was kept beneath 0.22 W/cm², i.e., below the level associated with thermal skin injury (35). Electrode temperature was monitored and the power was lowered automatically when the temperature of any electrode exceeded 41°C. This value is well below the threshold of 44°C, i.e., the lowest prolonged temperature that can cause thermal injury (34).

TTFields having the optimal frequency of 200 kHz for rat and human gliomas (see Fig. 2) and an intensity of 1–2 V/cm (peak) were used in the trial. TTFields were switched sequentially every 1 sec between two perpendicular directions; lateral and anterior–posterior, through two sets of insulated electrode pairs. Patients received treatment continuously until disease progression or for a maximum of 18 months. Treatment was applied daily for an average of 18 h per day.

Patient evaluation. Objective tumor assessment was performed by Gd-enhanced MRI according to a strictly defined protocol. MRI scanning was performed at trial entry within one week of NovoTTF-100A treatment initiation and after every treatment course (28–30 days). All scans were reviewed by a board certified radiologist (J.V.). The assessment of tumor response was based on criteria defined by Macdonald *et al.* (32). Study visits were performed once per week during the first month of treatment and monthly thereafter. The following examinations were carried out at each visit: Neurological evaluation, EKG, complete blood count with differential, chemistry panel, and coagulation studies. Adverse events occurring during treatment or up to 60 days after termination of therapy were scored according to the common toxicity criteria scale (version 3). Disease progression was not captured as a serious adverse event.

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Disruption of Cancer Cell Replication by Alternating Electric Fields

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ABSTRACT

Low-intensity, intermediate-frequency (100–300 kHz), alternating electric fields, delivered by means of insulated electrodes, were found to have a profound inhibitory effect on the growth rate of a variety of human and rodent tumor cell lines (Patricia C, U-118, U-87, H-1299, MDA231, PC3, B16F1, F-98, C-6, RG2, and CT-26) and malignant tumors in animals. This effect, shown to be nonthermal, selectively affects dividing cells while quiescent cells are left intact. These fields act in two modes: arrest of cell proliferation and destruction of cells while undergoing division. Both effects are demonstrated when such fields are applied for 24 h to cells undergoing mitosis that is oriented roughly along the field direction. The first mode of action is manifested by interference with the proper formation of the mitotic spindle, whereas the second results in rapid disintegration of the dividing cells. Both effects, which are frequency dependent, are consistent with the computed directional forces exerted by these specific fields on charges and dipoles within the dividing cells. *In vivo* treatment of tumors in C57BL/6 and BALB/c mice (B16F1 and CT-26 syngeneic tumor models, respectively), resulted in significant slowing of tumor growth and extensive destruction of tumor cells within 3–6 days. These findings demonstrate the potential applicability of the described electric fields as a novel therapeutic modality for malignant tumors.

INTRODUCTION

In the laboratory setting and in clinical practice, alternating electric fields show a wide range of effects on living tissues. At very low frequencies (under 1 kHz), alternating electric fields stimulate excitable tissues through membrane depolarization (1). The transmission of such fields by radiation is insignificant, and therefore they are usually applied directly by contact electrodes, although some applications have also used insulated electrodes. Some well-known examples of such effects include nerve, muscle, and heart stimulation by alternating electric fields (1, 2). In addition, low-frequency pulsed electric fields have been claimed to stimulate bone growth and accelerate fracture healing (3). However, as the frequency of the electric field increases above 1 kHz, the stimulatory effect diminishes. Under these conditions, although a greater fraction of the fields penetrates the cells, due to the parallel resistor-capacitor nature of all biological membranes, the stimulatory power greatly diminishes as the alternating cell membrane hyper-depolarization cycles are integrated such that the net effect is nulled. At very high frequencies (*i.e.*, above many MHz), although the integration becomes even more effective, a completely different biological effect is observed. At these frequencies tissue heating becomes dominant due to dielectric losses. This effect becomes more intense as frequency, field intensity, or tissue dissipation factor increases (4). This phenomenon serves as the basis for some commonly used medical treatment modalities including diathermy and radio frequency tumor ablation, which can be applied through insulated electrodes (5). Intermediate-frequency electric fields (*i.e.*, tens of kilohertz to megahertz) alternate too fast for causing nerve-muscle stimulation and involve only minute dielectric losses (heating). Such fields of low to moderate intensities are commonly considered to have no biological effect (4). However, a number of nonthermal effects of minor biological consequence have been reported even at low field intensities. These include microscopic particle alignment (*i.e.*, the pearl chain effect; Ref. 6) and cell rotation (7, 8). With pulsed electric fields of 10^3 V/cm and 100-ms pulse length, reversible pore formation appears in the cell membrane, a phenomenon usually called electroporation (9).

In the present study we show for the first time, to our knowledge, that very low-intensity (<2 V/cm), intermediate-frequency (100–300 kHz), alternating electric fields induced by insulated electrodes have specific inhibitory effects on dividing cells in culture. We demonstrate that applying these fields to cancerous cells leads to proliferation arrest and cell destruction. When applied to syngeneic mice tumor models, these tumor treating fields (TTFields) cause a significant reduction in tumor growth rate without any significant side effects.

MATERIALS AND METHODS

***In Vitro* Experimental Set Up.** Cultures were grown in standard culture dishes (4-well cell culture chambers; SN 138121; Nalge Nunc International). The TTFields were generated by pairs of 15-mm-long, completely insulated wires (P/N K-30-1000; VT Corporation; outer diameter, 0.5 mm; ethylene tetrafluoroethylene insulation thickness, 0.125 mm; dielectric breakdown, 1800 V/mil) fixed to the bottom of each dish at a distance of 1 mm from each other. The wires were connected to an oscillator (GFG8219A; Instek) and a high-voltage amplifier (A303; A. A. Lab Systems Ltd.) that generated the required sine-wave signals (range, 300–800 V). Cells were plated by carefully smearing 10 μl of DMEM (Biological Industries Ltd., Beit Haemek, Israel) containing 1.5×10^4 cells along the gap between the wires (Fig. 1A). After the cells settled and attached to the plate surface, 500 μl of DMEM were added to each culture dish, which was then transferred to a 5% CO_2 humidified incubator held at 36°C. The culture was incubated for a control period of 24 h before treatment. Culture medium was replaced manually every 24 h throughout the experiments. TTFields were then applied by connecting the wires to a high-voltage amplifier operated by a signal generator with frequency and amplitude controls. Finite element simulation of the TTFields generated between the wires demonstrated that the field in the vicinity of the cell culture was homogenous (not shown). Eleven different types of cancerous cell lines were subjected to TTFields. These included human melanoma (Patricia), glioma (U-118, U-87), Lung (H-1299), prostate (PC3), and breast (MDA231) cancerous cell lines as well as mouse melanoma (B16F1), rat glioma (F-98, C-6, and RG2), and mouse adenocarcinoma (CT-26) cell lines (all from American Type Culture Collection, except for Patricia, which was a generous gift from Dr. Ruth Halaban, Department of Dermatology, Yale University School of Medicine). In addition, a noncancerous cell line (BHK) was grown under conditions that stunt cell replication (0.1% FCS) and then subjected to TTFields. Also, segments of excised rat mesentery and diaphragm were subjected to the fields *in vitro*. Colorimetric cell counts were made every 24 h after seeding using the standard 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide method to measure cell proliferation as described previously (10) using cell proliferation assay kit (Biological Industries, Beit Haemek, Israel). In brief, culture media was replaced with 0.2 ml of preheated 2,3-bis(2-methoxy-4-nitro-5 sulfophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide reagent and incubated for 1 h at 37°C in a 5% CO_2 incubator. After incubation and gentle stirring,

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0.15 ml of the reaction solution was transferred to a 96-well plate (SN 92696; TPP, Trasadingen, Switzerland). The absorbance of the samples was then read with a spectrophotometer (Tecan ELISA Reader; 450 nm). The colorimetric measurements at each time point were normalized to the measurement performed immediately before beginning of treatment. To verify that the colorimetric assessments were accurate, direct visual cell counts were performed on sample culture dishes. At the optic densities used (0.2–2), optic density was linearly related to the number of cells in the culture dishes ($n = 10$; $r^2 = 0.99$). The growth rate of both treated (GR_t) and control cultures (GR_c) was calculated for each experiment by plotting the optic density values on a logarithmic scale and fitting a linear regression line to the values. The growth rate for each culture dish was the slope of this linear regression. The therapeutic enhancement ratio (TER) was calculated as the ratio of the decrease in the growth rate of treated cells compared with the growth rate of control cells [$(GR_c - GR_t)/GR_c$]. Thus, if the increase in the number of treated cells is equal to that of the controls, TER = 0; if the increase in cell number is smaller in the treated cultures than in the controls, TER > 0; and if the number of cells in the treated cultures decreases absolutely, TER > 1.

In time-lapse microphotography experiments, cell lines were grown on a 35-mm standard culture dish (SN 430165; Corning Inc.) by plating 3×10^4 cells in 2.5 ml of DMEM with 25 mM HEPES. The Petri dish temperature was controlled at 34°C (B16F1) or at 37°C (all other cell lines). Subsequently, two parallel insulated wires were positioned on the bottom of the dish with 1 mm distance between, through which TTFields were applied. The entire set-up was placed on an inverted microscope (Eclipse TS-100; Nikon) and video microphotographs at ×200 magnification were taken with a standard VCR camera (Handicam X 320; Sony). Photographs were captured using a personal computer every 60–120 s for 6–10 h/culture.

Fluorescent Labeling of α-Tubulin, Actin, and DNA. Mouse melanoma cells were grown on coverslips and subjected to TTFields for 24 h. After treatment, the medium was removed, and the cells were washed in a buffer solution [10 mM 4-morpholineethanesulfonic acid, 150 mM NaCl, 5 mM EGTA, 5 mM $MgCl_2$, and 5 mM glucose (pH 6.1)], permeabilized, and fixed with 0.5% Triton X-100 and 0.25% glutaraldehyde (Sigma) for 5 min and then post-fixed with 1% glutaraldehyde for 20 min. Subsequently, the cells were washed in PBS and 1 mM sodium borohydride (Sigma) to eliminate autofluorescence. The coverslips were then incubated with a primary antibody clone for α-tubulin (DM1A; Sigma) for 30 min, washed, and incubated for 30 min with a secondary antibody (Alexa Fluor 488 goat antimouse IgG; Molecular Probes). Rhodamine-conjugated phalloidin (Sigma) was added with the secondary antibody to stain actin filaments. The cells were then washed and incubated with 4′,6-diamidino-2-phenylindole (Molecular Probes) to stain the DNA. After staining, the coverslips were mounted and viewed with a fluorescence microscope at ×630 magnification and photographed.

Electric Field Measurement. The electric field intensity in the culture medium was measured by means of a probe, consisting of two (0.25 mm in diameter) insulated wires with exposed tips 0.5 mm apart, that was dipped in the culture medium. The wires were connected to a high-input impedance differential amplifier that translated the waveform amplitude into a calibrated steady voltage that was digitally recorded. Field intensities throughout the manuscript are expressed in peak voltage amplitude per centimeter (V/cm). Care was taken to eliminate any pickup from the field outside the culture medium. Continuous field monitoring could also be made by measuring the potential drop across a 100Ω resistor placed in series with one of the field-generating wires. The voltage drop on this resistor was linearly correlated to the field intensity ($r^2 = 0.96$). To verify that the experimental setups were not exposed to any significant magnetic fields, the electromagnetic radiation in the immediate vicinity of the treated cultures was measured using a loop antennae (EMCO 6507 1 kHz to 30 MHz) connected to a spectrum analyzer (Anritsu 9 kHz to 2.2 GHz). The electromagnetic radiation in the 100–300-kHz range within the incubators containing treated culture dishes was found to be 10^{-12} Tesla and within animal cages containing TTField-treated mice, 10^{-14} Tesla, *i.e.*, negligible.

Finite Element Simulations of Electric Field Distribution. The calculations of the electric field within the cells are based on finite element mesh (11), using a simplified description of the cell morphology (see Fig. 7). In all calculations, the dielectric constant of both the cytoplasm and medium was 80, their conductance was 0.3 S/m, the cell diameter was 10 μm, and the membrane thickness was 3 nm (with a dielectric constant of 3). The electric field intensity was mapped within the cell, based on the amplitude (1 V/cm), frequency (100 kHz) and waveform (sine) of the electric field applied to the cell culture. The force exerted by an inhomogeneous field, such as that created inside the cells on a single tubulin dimer, was calculated based on the direct interaction between the electric field and the dipole. The force exerted on a microscopic polarizable organelle was calculated by the following equation (12):

$$\langle \vec{F} \rangle = 2\pi r^3 \epsilon_m \mathrm{Re}[K(\omega)] \vec{\nabla} E_{RMS}^2 \tag{1}$$

where $\langle \vec{F} \rangle$ is the expectation value of the force vector, *Re* symbolized the real component of the variable, $\vec{\nabla}$ is the divergence of the variable, ϵ_m is the cytoplasm dielectric constant, r is the tubulin dimer length or particle radius, E_{RMS} is the RMS value of the electric field, and $K(\omega)$ is the Clausius-Mossotti factor:

$$K(\omega) = \frac{\epsilon_p^* - \epsilon_m^*}{\epsilon_p^* + 2\epsilon_m^*}$$

$$\epsilon^* = \epsilon - j \cdot \frac{\sigma}{\omega} \tag{2}$$

where ϵ^*_p, ϵ^*_m are the complex dielectric constants of the particle and cytoplasm respectively, each of which is calculated from the dielectric constant (ϵ) and conductance (σ) as a function of frequency (ω). $K(\omega)$ in this case is always positive at the relatively low frequencies used (*i.e.*, 100 kHz), assuming that at these frequencies, $\epsilon_p \gg \epsilon_m$. This means that the force acting on a polarizable particle will always act in the direction of the convergence of the electric field lines. The terminal velocity of particles due to these forces was calculated using Stoke's law.

***In Vivo* Experimental Setup.** TTField treatment was applied by means of 10-mm-long pairs of parallel, insulated wires (outer diameter, 0.5 mm; insulation thickness, 0.125 mm; Teflon) placed intradermally on the back of a mouse. Another pair of identical wires was placed parallel to the first pair in each mouse, with an interval of 5 mm between the pairs. Cell line inoculums were injected (4 μl; 3×10^5 cells) intradermally in between the two members of each pair of implanted wires. Only one pair was then connected to a voltage amplifier to apply 100 kHz of TTFields treatment to one tumor. The other pair of wires was left disconnected, and the tumor between them served as a paired control of the treated tumor (see Fig. 1B). Tumors were measured using a caliper. Tumor size was calculated by multiplying maximal tumor length by maximal tumor width. Animal experiments were conducted in accordance with the Technion—Israel Institute of Technology guidelines for the care of laboratory animals.

RESULTS

Effect of TTFields on Cells in Culture. More than 500 culture dishes were exposed to TTFields. The number of cells in each treatment dish was assessed periodically using colorimetric determination (as described in "Materials and Methods"). Because under control conditions, most of the cell lines had doubling times of less than 24 h (range, 17–24 h; except for PC-3 for which the doubling time was 73 h), treatment duration was at least 24 h. Exposure began 24 h after seeding and was continued for up to 72 h. In all cell lines tested, 24-h exposure to TTFields at 100 kHz (at an intensity of 1.0–1.4 V/cm) caused significant inhibition of cell proliferation (TER range, 0.14–0.96; $P < 0.05$; Fig. 1C). This effect lasted beyond the exposure time of the cells to TTFields. In fact in some experiments (*e.g.*, malignant melanoma), culture growth was stunted for as long as 72 h after TTField exposure was terminated (Fig. 2A).

We next checked whether nonreplicating cultures and tissues are affected by TTFields. BHK cultures were maintained in low-serum (0.1% FCS) conditions to slow their replication rate. These cultures were then exposed to 100 kHz of TTFields (at an intensity of 1.2 V/cm) for 24 h. No significant difference in cell number between control and TTField-treated cultures was observed under these con-

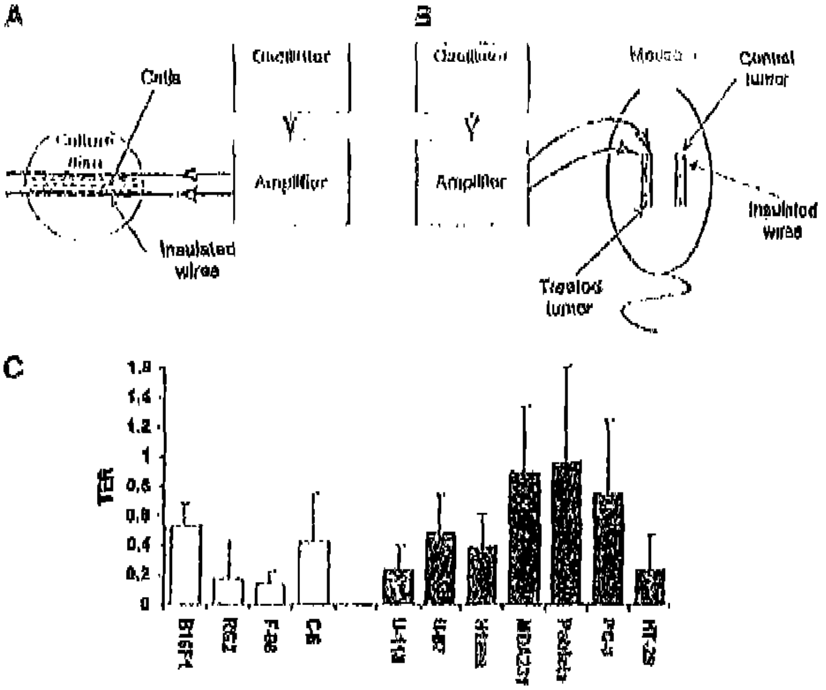

Fig. 1. Schematic representations of experimental setups in vitro (A) and in vivo (B) are shown. C, TTFields inhibit the growth of cancerous cell lines in vitro. Cultures were exposed to 100-kHz TTFields at an intensity of 1–2 V/cm. Ordinate, TER, i.e., the ratio of the decrease in the growth rate of treated cells compared with the growth rate of control cells ($(GR_c - GR_t)/GR_c$). In all four animal cell lines (□) and seven human cell lines (■) tested, the ratio is greater than 0, indicating an inhibition in the growth rate of the treated cultures compared with temperature-matched controls. All effects were statistically significant ($P < 0.05$; Student's t test).

ditions ($P = 0.97$). After returning these cultures to normal media (10% FCS), normal replication resumed both in cultures exposed to TTFields and in control cultures. We also tested the effect of TTField treatment on the number of viable cells in nonreplicating tissues dissected from rats. Four segments of rat mesentery and four segments of rat diaphragm were exposed to 100 kHz of TTFields at an intensity of 1.2 V/cm for 24 h. No differences were observed between the number of viable cells in both types of treated tissues compared with control tissues (mesentery, $P = 0.3$; diaphragm, $P = 0.54$).

To test the relationship between TTField intensity and inhibition of cell proliferation, mouse melanoma (B16F1) and rat glioma (F-98) cell lines were exposed to TTFields of different intensities between 1 and 2.5 V/cm. The inhibitory effect of TTFields on cell proliferation increased as intensity was raised (Fig. 2B) until complete proliferation arrest was achieved at intensities of 1.4 and 2.25 V/cm in melanoma and glioma cells, respectively.

The effects of TTFields are expected to be frequency dependent in view of the dependence of cell membrane electric impedance on frequency (due to the cell membrane capacitance). These changes in impedance render the fraction of field penetrating the cells a function of frequency. Therefore, we tested the frequency dependence of the inhibitory effect of TTFields on growth rate of cultured melanoma (B16F1) and glioma (F-98) cells. Comparison between the efficacy of the TTFields at different frequencies was performed by normalizing the TER to the electric field intensity. As seen in Fig. 2C, the inhibitory effect of TTFields was frequency dependent. Interestingly, the frequency at which maximal inhibition was achieved differed between cell types (120 kHz *versus* ~200 kHz for melanoma and glioma, respectively).

The Effects of TTFields on Cellular and Molecular Processes in Proliferating Cells. To gain insight into the cellular processes by means of which TTFields affect cell proliferation, time-lapse microphotography was performed while TTFields were applied to mouse melanoma cultures (see "Materials and Methods"). Several unique processes became evident in time-lapse microphotography of TTField-treated cultures. The most pronounced phenomenon was prolongation of mitosis. In the treated cells, mitosis seemed to begin normally but was prolonged for variable periods of time before completing cleavage into two daughter cells. Fig. 3A shows an exemplary mitosis in a TTFields-treated cell. As seen in the treated cell, mitosis was not complete within 3 h. Due to this proliferation arrest, in treated cultures, mitosis lasted on average 124 ± 91 min (mean ± SD, $n = 53$; range, 40–541 min), whereas under control conditions, average mitosis duration was 62 ± 8 min from cell rounding to cytokinesis (mean ± SD, $n = 12$; range, 47–78 min). This prolongation is statistically significant ($P < 0.01$, Mann-Whitney *U* test).

The second major phenomenon, seen in the TTField-treated melanoma cultures, was that one-fourth of cells undergoing mitosis were destroyed as the formation of the cleavage furrow approached complete cell separation. During this process, the cell membrane ruptured, and many small membrane blebs formed, resembling post-mitotic apoptotic cell death (13). Two exemplary cells undergoing such destruction are shown in Fig. 3, *B* and *C*. Destructive effects were observed only in mitotic cells, whereas quiescent cells remained morphologically and functionally intact.

The third phenomenon, seen only in TTField-treated cultures, was nuclear rotation. In early mitosis, after cell rounding, nuclei could be seen rotating within the cell. A full rotation lasted on average 15 min. This effect resembles the whole-cell rotation previously described during exposure to intermediate-frequency alternating electric fields (7, 8).

A fundamental characteristic of electric fields is that at any point in space, they have a defined orientation corresponding to the direction of the force they exert on charges and polar elements. With regard to the latter, the force exerted by the field is maximal when the dipole is oriented in the direction of the field. With regard to the above, there are two main structural differences between quiescent and dividing cells. One is that the latter contain highly polar, spatially oriented microtubules and that they develop a directional, hourglass-shaped cell morphology during the cytokinesis phase. In view of these facts, one may expect that the electric field forces will have maximal effect

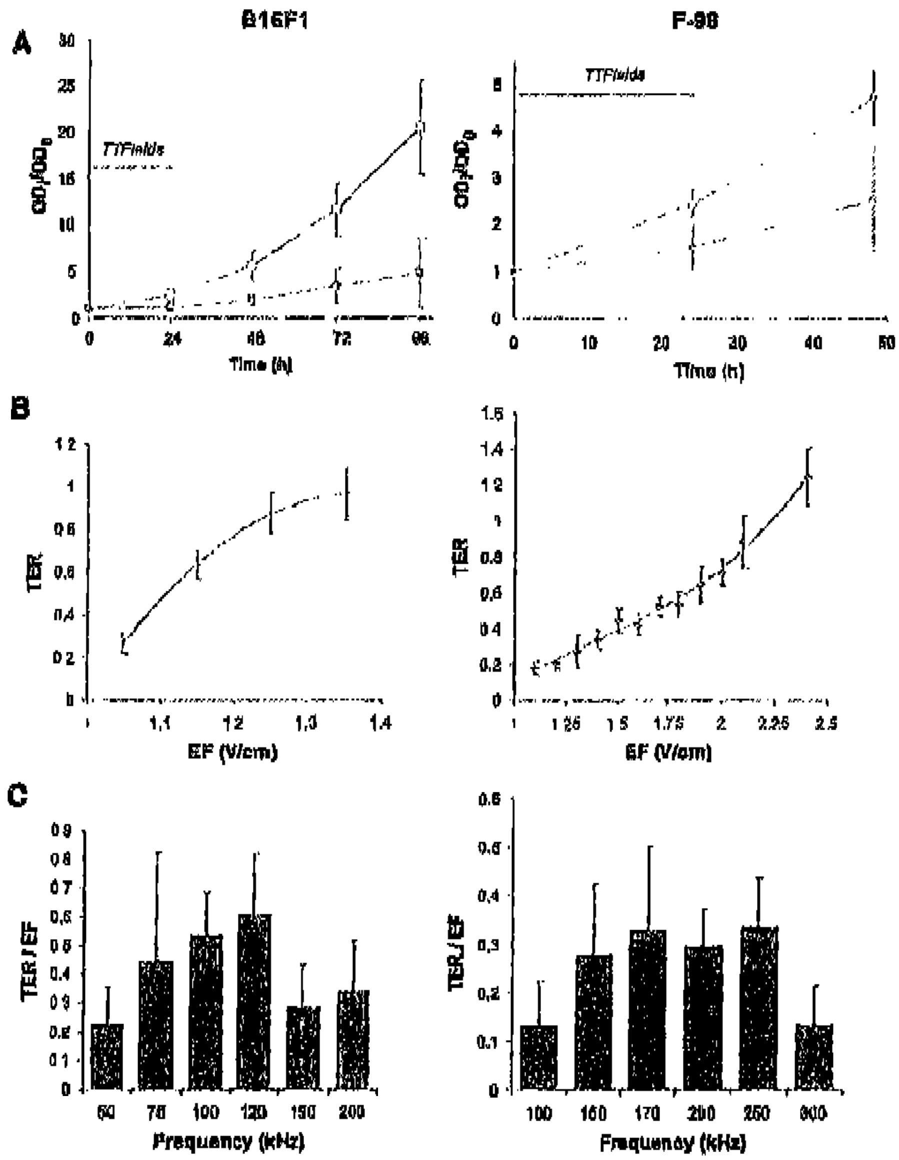

Fig. 2. Time, field frequency, and intensity dependence of the effect of TTFields on malignant melanoma (B16F1, *left column*) and glioma cell (F-98, *right column*) proliferation. *A*, the number of cells in untreated cultures (control; □) as compared with cultures treated with TTFields (■). The number of cells at each time point (OD_t) was normalized by the number of cells in the culture *before* initiation of treatment (OD_0). The number of control cells is seen to roughly double every 24 h throughout the experiment. TTFields were applied for 24 h continuously (*solid lines*) at 100 kHz in the melanoma cultures and at 200 kHz in the glioma cultures. The increase in the number of treated melanoma (*left*) and glioma (*right*) cells over time is significantly smaller than control cells ($P < 0.001$). *B*, the effect of 24-h exposure to TTFields of increasing intensities. The magnitude of the effect is expressed using the *TER*. The inhibitory effect of the TTFields on proliferation increases with intensity in both cell types. Complete proliferation arrest (TER = 1) is seen at 1.35 and 2.25 V/cm in melanoma and glioma cells, respectively. *EF*, electric field. *C*, change in the melanoma (*left*) and glioma (*right*) growth rate after 24 h of exposure to TTFields of different frequencies is normalized to the field intensity (*TER/EF*). A window effect is seen with maximal inhibition by TTFields at 120 kHz in melanoma cells and at ~200 kHz in glioma cells. Data are mean + SE.

on the mitotic process when it is oriented along the lines of force of the field. To investigate this point, we fixed melanoma cell cultures and stained them with toluidine blue, immediately after 24 h of TTField treatment, to demonstrate mitoses and to distinguish vital from damaged or dead cells. The live and damaged mitotic cells (at the time of fixation) were grouped according to the orientation of their cleavage axis relative to the electric field direction. The cells were counted separately in each of four equal sectors that form angles of 0°, 45° (two sectors, 45 and 135), and 90° relative to the field direction. As seen in Fig. 4*A*, the live cells were randomly distributed in all sectors. In contrast, a much higher proportion of the damaged cells had their axis of division oriented along the field: 56% at 0° *versus* an average of 15% in each of the other orientations. Surprisingly, the number of cells per unit area in the two 45° sectors was found to be one-half that in the 0° sector. This finding may serve as an indication of an additional effect of TTFields: orientation of the cell division in the field direction. The cells in each of the above spatially oriented defined groups were further divided according to stages of mitosis at the time of fixation. At all stages, a higher fraction of damaged cells had their axis of division oriented along the field. Moreover, 74% of the parallel oriented cells were damaged while being in metaphase (Fig. 4*B*).

The spatially organized mitotic spindle, which forms in dividing cells, consists of microtubules that have very large electric dipole moments (14) and may therefore be disoriented by the forces of the electric fields (15, 16). Actin filaments are also polar, however, they have no defined spatial orientation within the cells and are therefore not expected to be significantly affected by the fields. This prompted us to test whether TTFields disrupt mitosis by interfering with the normal formation, orientation, and movement of microtubules as compared with actin filaments as follows: Melanoma cell cultures were treated with TTFields for 24 h. After treatment, the cells were fixated, stained with monoclonal antibodies directed against microtubules and actin filaments, as well as for DNA, and thereafter studied with fluorescence microscopy (see "Materials and Methods"). In control cultures, 95% of cells undergoing mitosis exhibited the normal stages of mitosis with intact mitotic spindles. However, in TTField-treated cultures, more than one-half of the mitoses were abnormal.

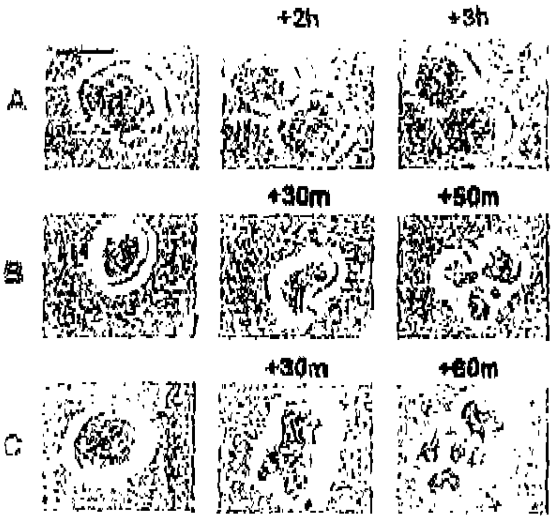

Fig. 3. Time-lapse microphotography of malignant melanoma cells exposed to TTFields. A, an example of a cell in mitosis arrested by TTFields. Contrary to normal mitosis, the duration of which is less than 1 h, the depicted cell is seen to be stationary at mitosis/prometaphase for 3 h. B and C, two examples of disintegration of TTField-treated cells during cytokinesis. Three consecutive stages are shown: cell rounding (left); formation of the cleavage furrow (middle); and cell disintegration (right). Scale bar = 10 μm.

Fig. 5 shows examples of the different forms of abnormal mitosis seen under TTField treatment. These included polyploid cells in prophase, ill-separated, multi-spindled and single-spindled cells in metaphase, asymmetric anaphases, and a large proportion of cells in metaphase (>20%) with rosette shaped chromosome assemblies. The normal and abnormal stages of mitosis in control and TTField-treated cultures are summarized and compared in Fig. 5G. In general, these abnormalities may serve as an indication of interference of TTFields with the normal behavior of the microtubules. In contrast, staining for actin filaments showed no difference between TTField-treated and control cultures.

Effect of TTFields on Tumors *in Vivo*. To test whether TTFields are effective in destroying tumor cells *in vivo*, we tested their effect on two animal tumor models: C57BL/6 mice inoculated intradermally with malignant melanoma cells (B16F1) and BALB/c mice inoculated intradermally with adenocarcinoma cells (CT-26). TTFields were generated between implanted (intradermal) wholly insulated wires placed on both sides of the tumor (see Fig. 1B). Mice with implanted electrodes were treated for 3–6 days continuously beginning 1 day after cell line inoculation. We found that 100–200 kHz of TTFields at low intensities of <2 V/cm effectively inhibited malignant melanoma growth compared with the growth of nontreated control tumors. Photographs of examples of treated and nontreated malignant melanoma tumors are given in Fig. 6 for comparison. Treated tumors were significantly smaller than control tumors at the end of treatment (average treated tumor size was 47% of control tumor size; $n = 78$ mice, $P < 0.001$; Student's t test). Histopathological analysis of treated tumors showed extensive necrosis with aggregations of karyorrhectic and karyolytic debris (Fig. 6F). To test whether TTFields are effective on different tumor types, BALB/c mice with intradermal adenocarcinomas were treated with the same field parameters. Photographs of examples of such a treated and a nontreated adenocarcinoma tumors are provided for comparison in Fig. 6B. The average effect of TTFields on adenocarcinoma carrying mice was less dramatic than that seen for malignant melanoma (average treated tumor size was 73% of control tumor size at the end of treatment; $n = 14$ mice). After treatment, the tumors and their adjacent tissues were fixated, stained with H&E, and analyzed histopathologically. No damage to the surrounding tissues was detected.

DISCUSSION

In this study, we have shown that when properly tuned, very low-intensity, intermediate-frequency electric fields (TTFields) stunt the growth of cancerous cells. We have demonstrated this inhibitory effect in all proliferating cell types tested, whereas, nonproliferating cells and tissues were unaffected. Interestingly, different types of cancerous cells showed specific intensity and frequency dependences of TTField inhibition. We have demonstrated that two main processes occur at the cellular level during exposure to TTFields: arrest of proliferation and cell destruction. The damage caused by TTFields to these replicating cells was shown to be dependent on the orientation of the division process in relation to the field vector, indicating that this effect is nonthermal. Indeed, temperature measurements made within culture dishes during treatment and on the skin above treated tumors *in vivo*, showed no significant elevation in temperature compared with control cultures/mice. Also, TTFields caused the dividing cells to orient in the direction of the applied field in a manner similar to that described in cultured human corneal epithelial cells exposed to constant electric fields (17). At the subcellular level, we have found evidence indicating that TTFields disrupt the normal polymerization-depolymerization process of microtubules during mitosis. Indeed, the described abnormal mitotic configurations seen after exposure to

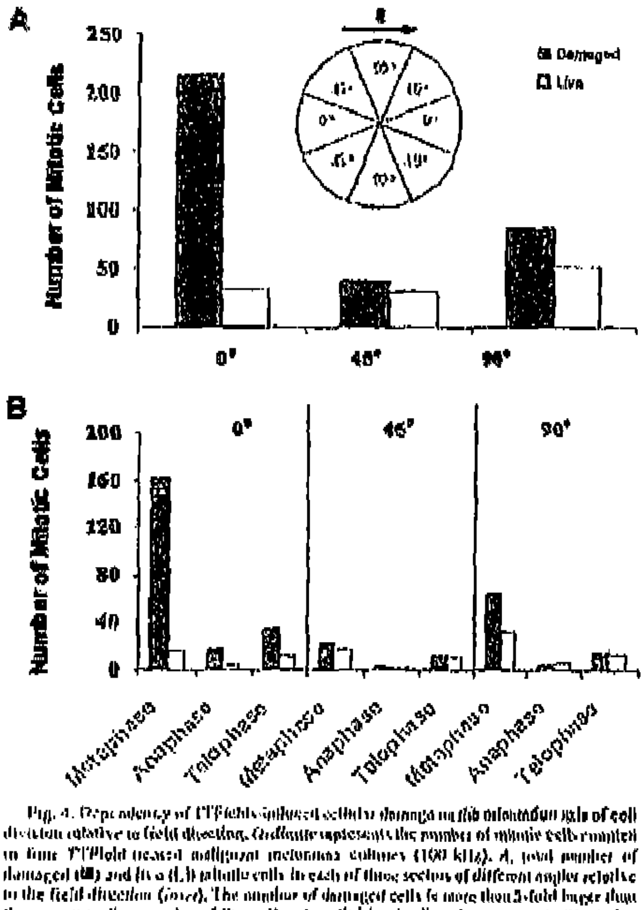

Fig. 4. Dependency of TTFields-induced cellular damage on the orientation axis of cell division relative to field direction. Ordinate represents the number of mitotic cells counted in four TTField treated malignant melanoma cultures (100 kHz). A, total number of damaged (■) and live (□) mitotic cells in each of three sectors of different angles relative to the field direction (inset). The number of damaged cells is more than 5-fold larger than the corresponding number of live cells when division is aligned at or close to 0° relative to the electric field direction. In sectors of other angles, the number of damaged cells only slightly exceeds the live ones. Note that because the 45° area is double that of each of the other two sectors, the number of cells presented in this orientation was halved. B, dividing cell sensitivity to fields of different orientation at different stages of mitosis. When cell division axis is aligned at 0° to the electric field, the number of damaged cells (■) is significantly larger than that of intact cells (□) at all three phases of mitosis. However, the highest number of damaged cells in this orientation is seen at metaphase (8-fold more than intact cells).

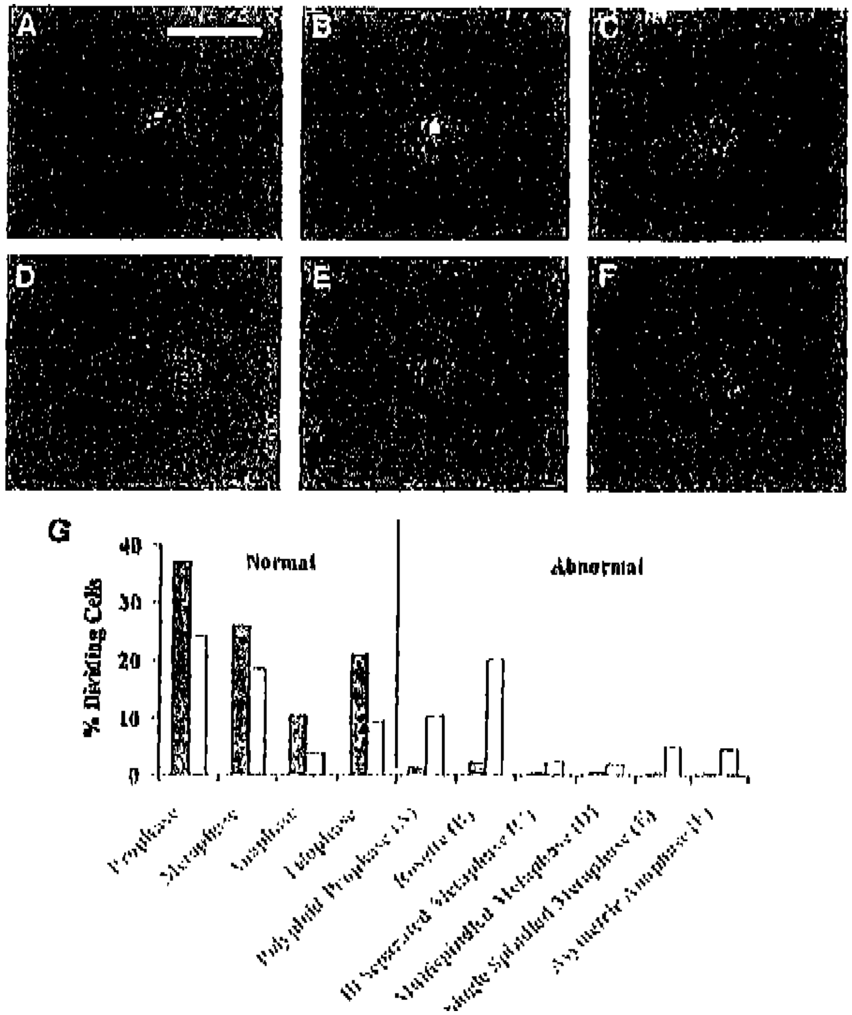

Fig. 5. Immunohistochemical staining of abnormal mitotic figures in TTFields-treated cultures. Malignant melanoma cultures ($n = 4$) were treated for 24 h at 100 kHz and then stained with monoclonal antibodies for microtubules (*green*), actin (*red*), and DNA (*blue*). The photomicrographs show exemplary abnormal mitoses including: polyploid prophase (*A*); rosette (*B*); ill separated metaphase (*C*); multispindled metaphase (*D*); single-spindled metaphase (*E*); and asymmetric anaphase (*F*). *G*, the percentage of treated (□) and control (■) mitotic cells in each of the normal and abnormal phases of mitosis.

TTFields are similar to the morphological abnormalities seen in cells treated with agents that interfere directly (18, 19) or indirectly (20–22) with microtubule polymerization (*e.g.*, Taxol).

To explain how TTFields cause orientation-dependent damage to dividing cancerous cells and disrupt the proper formation of the mitotic spindle, we modeled the forces exerted by TTFields on intracellular charges and polar particles using finite element simulations (see "Materials and Methods"). We identified two main mechanisms by means of which the electric fields may affect dividing cells. The first relates to the field effect on polar macromolecule orientation. Within this framework, during the early phases of mitosis, *i.e.*, in pre-telophase, when tubulin polymerization-depolymerization drives the proliferation process, the electric field forces any tubulin dimers, positioned further than 14 nm away from the growing end of a microtubule, to orient in the direction of the field (Fig. 7*A*). This force moment, (10^{-5} pN) acting on the dimers, is sufficient to interfere with the proper process of assembly and disassembly of microtubules that is essential for chromosome alignment and separation (23). This effect can explain the mitotic arrest of TTField-treated cells (24). The second mechanism, which interferes with cell division and is most likely to play an important role in cell destruction, becomes dominant during cleavage. As seen in the simulations depicted in Fig. 7*B*, the electric field within quiescent cells is homogeneous, whereas the field inside mitotic cells, during cytokinesis, is not homogenous. We see an increased field line concentration (indicating increased field intensity) at the furrow, a phenomenon that highly resembles the focusing of a light beam by a lens. This inhomogeneity in field intensity exerts a unidirectional electric force on all intracellular charged and polar entities, pulling them toward the furrow (regardless of field polarity). For example, for a cleavage furrow that reached a diameter of 1 μm in an external field of only 1 V/cm, the force exerted on the microtubules is in the order of 5 pN. This magnitude is compatible with the reported forces necessary to stall microtubule polymerization that is 4.3 pN (25). With regard to other particles such as cytoplasmatic organelles, they are polarized by the field within dividing cells. Once polarized, the forces acting on such particles may reach values up to an order of 60 pN resulting in their movement toward the furrow at velocities that may approach 0.03 μm/s. At such velocity, cytoplasmatic organelles would pile up at the cleavage furrow within a few minutes, interfering with cytokinesis and possibly leading to cell destruction. We also found that the electric forces acting on intracellular particles are maximal when the axis of division is aligned with the external field. This is consistent with the dependence of the destructive effect of TTFields on the angle between division axis and the field (Fig. 4). In addition, the calculated dependence of the magnitude of this force on frequency (data not shown) is consistent with the experimentally determined frequency dependence of the

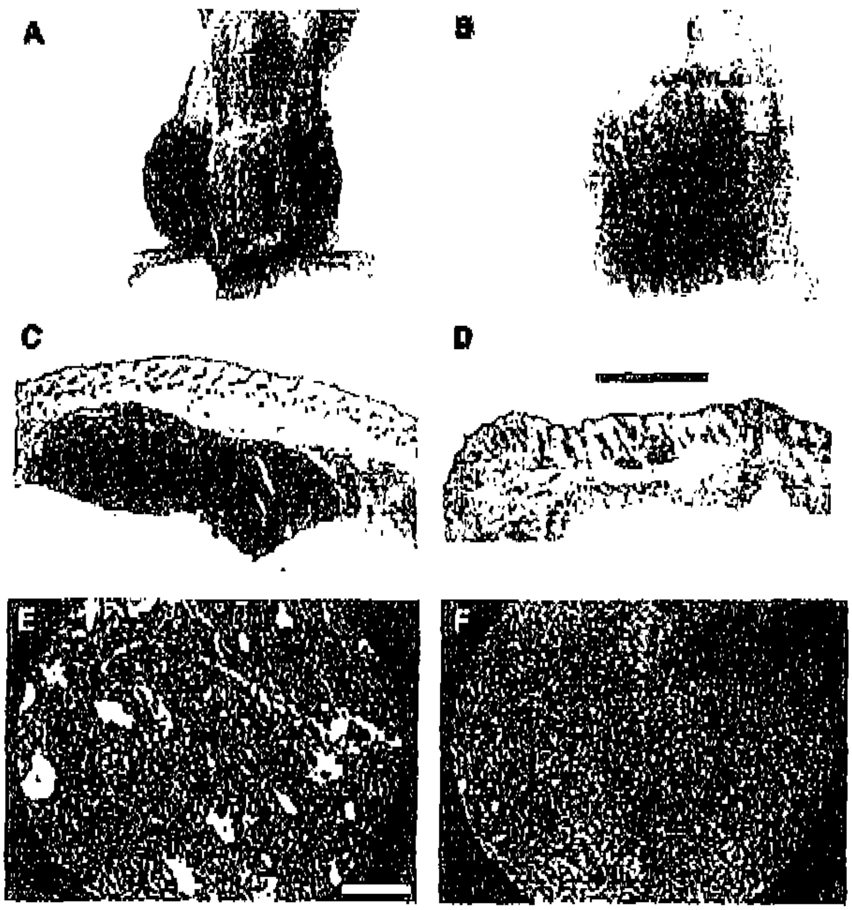

Fig. 6. *In vivo* effects of TTFields on intradermal tumors in mice. Malignant melanoma (*A*) and adenocarcinoma (*B*) tumor cells were injected in two parallel locations intradermally on the back of each mouse. Only the tumor on the left side of the mouse was treated. After 4 days of TTFields treatment (at 100 kHz), no tumor can be discerned on the treated side, whereas on the untreated side a large tumor has grown. *C–F*, histological sections of TTFields-treated intradermal melanoma *versus* a control (untreated) melanoma on the same mouse. *C*, after H&E staining, a large (5 mm diameter) nodule of melanoma cells can be seen in the dermis of the control tumor (×40). Note that due to the large size of the tumor, its deep portion has been lost in preparation. *D*, treated tumor; only two small (<0.4 mm diameter) nodules are present (*scale bar* = 0.5 mm). The nontumor structures of the dermis are morphologically intact. *E*, control tumor; malignant melanoma cells appear intact and viable (×200). (*Scale bar* = 100 μm). *F*, only necrotic tissue and cellular debris are seen in the treated tumor.

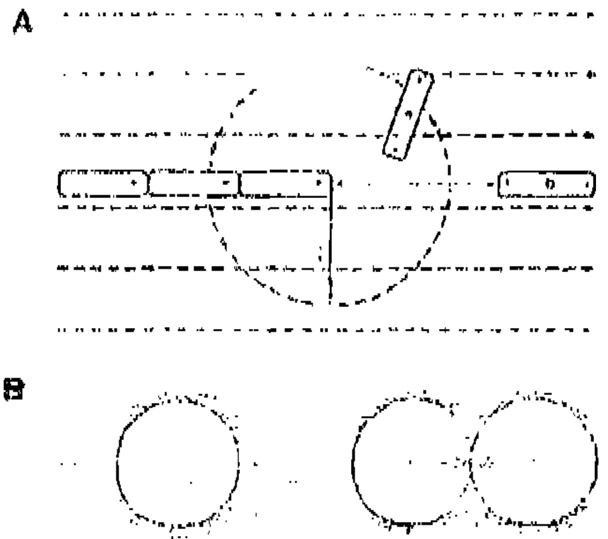

Fig. 7. *A*, schematic representation of two tubulin dimers positioned near the tip of an elongating microtubule in a dividing cell. The force that a 1-V/cm extracellular TTField exerts on a tubulin dimer located less than 14 nm away from the microtubule (*a*) is smaller than the force exerted by the polar microtubule tip, and therefore it will align according to the field generated by the microtubule. In contrast, dimers farther than 14 nm from the end of the microtubule (*b*) are aligned by the forces of the TTFields (*dashed lines*) in a direction that may not be compatible with the polymerization-depolymerization process. *B*, finite element mesh simulation of the lines of force of the electric field inside a quiescent cell (*left*) and a cell undergoing mitosis cytokinesis (*right*). The diameter of the cells in the simulations was 10 μm and membrane thickness 5 nm. Inside the quiescent cell, the electric field is totally uniform (equal distances between the lines of force). In contrast, in the dividing cell, the field is inhomogeneous—the field intensity (*line density*) increases toward the cleavage furrow.

inhibitory effect of TTFields on melanoma and glioma cell proliferation (Fig. 2C).

In conclusion, we have demonstrated that TTFields inhibit both the proliferation of malignant cells in culture and the growth of tumors in mice while showing no general side effects or local histopathological damage. The mechanism of action of the fields is, at least in part, dependent on disruption of the microtubules of the mitotic spindle and the electric forces resulting from focusing of the field in the dividing cells. The highly specific effects of these fields on dividing cells, together with the relative ease of applying them, focusing them, and screening from them, make them an attractive candidate to serve as a novel treatment modality for cancer.

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TTFields alone and in combination with chemotherapeutic agents effectively reduce the viability of MDR cell sub-lines that over-express ABC transporters

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Abstract

Background: Exposure of cancer cells to chemotherapeutic agents may result in reduced sensitivity to structurally unrelated agents, a phenomenon known as multidrug resistance, MDR. The purpose of this study is to investigate cell growth inhibition of wild type and the corresponding MDR cells by Tumor Treating Fields - TTFields, a new cancer treatment modality that is free of systemic toxicity. The TTFields were applied alone and in combination with paclitaxel and doxorubicin.

Methods: Three pairs of wild type/MDR cell lines, having resistivity resulting from over-expression of ABC transporters, were studied: a clonal derivative (C11) of parental Chinese hamster ovary AA8 cells and their emetine-resistant sub-line Emt[R1]; human breast cancer cells MCF-7 and their mitoxantrone-resistant sub lines MCF-7/Mx and human breast cancer cells MDA-MB-231 and their doxorubicin resistant MDA-MB-231/Dox cells. TTFields were applied for 72 hours with and without the chemotherapeutic agents. The numbers of viable cells in the treated cultures and the untreated control groups were determined using the XTT assay. Student t-test was applied to asses the significance of the differences between results obtained for each of the three cell pairs.

Results: TTFields caused a similar reduction in the number of viable cells of wild type and MDR cells. Treatments by TTFields/drug combinations resulted in a similar increased reduction in cell survival of wild type and MDR cells. TTFields had no effect on intracellular doxorubicin accumulation in both wild type and MDR cells.

Conclusions: The results indicate that TTFields alone and in combination with paclitaxel and doxorubicin effectively reduce the viability of both wild type and MDR cell sub-lines and thus can potentially be used as an effective treatment of drug resistant tumors.

Background

Multidrug resistance (MDR) [1] is encountered when cancer cells are exposed to chemotherapeutic agents for a few replication cycles. It is manifested in reduced sensitivity to both the specific chemotherapy as well as to a number of structurally unrelated agents. This phenomenon obviously poses a serious impediment to successful chemotherapy. Three decades of multidrug resistance research have identified a number of mechanisms by means of which cancer cells elude the effects of chemotherapeutic agents. The most often encountered MDR is the one resulting from over-expression of ATP-binding cassette transporters such as P-glycoprotein (MDR1), multidrug resistance-associated protein-1 (MRP1), and the breast cancer resistance protein (BCRP) [1-3]. These transporters, that recognize substrates of diverse chemical nature, lower the intracellular concentration of these substrates and are normally involved in detoxification [4,5].

MDR can potentially be overcome by the use of antitumor modalities that are not involved in membrane transport, for example, anti-angiogenic agents and physical

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modalities such as radiotherapy, heat and electric fields. Different types of electric fields were reported to inhibit cancer cell proliferation and cause cancer cell destruction, for example: exposure of cancer cells to low amplitude DC currents [6], low intensity, low frequency (50 Hz) AC currents [7] and the intermediate frequency (100-300 kHz) alternating electric fields, termed TTFields [8-12].

TTFields are a new physical cancer treatment modality that has recently been demonstrated to be highly effective when applied to cell cultures, animal cancer models, as well as patients suffering from locally advanced and/or metastatic solid tumors [8-12]. TTFields are alternating electric fields of low intensity (1-3 V/cm) and intermediate frequency (100 - 300 kHz) that are generated by special insulated electrodes applied to the skin surface. These specially tuned fields have no effect on quiescent cells while having an anti-proliferation and destructive effect on mitotic cells. This effect is due to the fact that during cytokinesis, TTFields exert forces that move charged or polar macromolecules and organelles towards the narrow neck, separating the newly forming daughter cells [8,9]. They also interfere with the polymerization processes of the microtubule spindle during cell division. Thus, TTFields disrupt the cell structure, inhibit cell division and result in cell death. In contrast to most anti-cancer agents, TTFields are not associated with any meaningful systemic toxicity [9-12]. Furthermore, it was recently shown that TTFields may be used clinically, not only as an anti-proliferation agent, but also as effective adjuvant to currently used chemotherapeutic agents [9].

In view of the above, the target of the present study was to test the possibility of using TTFields for treating multidrug resistant cancerous and non cancerous cell lines, both as a standalone treatment and in combination with chemotherapy.

Methods

Materials

All cell culture media, serum and media supplements were obtained from Biological Industries, Beth Haemek, Israel. All drugs and chemical agents were obtained from Sigma.

Cell lines

The following cell lines and their drug resistant derivatives were used: A clonal derivative (C11) of parental Chinese hamster ovary AA8 cells and their emetine-resistant sub-lines Emt[R1] cells having ATP dependent MDR1 type drug resistance [13], a kind gift from Prof. G. Eytan Dept. of Biology, Technion, Haifa, Israel; Human breast cancer wild type MCF-7 cells, obtained from ATCC and their mitoxantrone-resistant sub-lines MCF-7/Mx having ABCG2 transporter [14], a kind gift from Prof. M. Liscovitch, Dept. of Biological Regulation Weizmann Institute of Science, Rehovot, Israel; Human breast cancer wild type MDA-MB-231 cells obtained from ATCC and from which doxorubicin resistant MDA-MB-231/Dox cells were developed in our laboratory using a stepwise increase in drug concentration protocol. This procedure is identical with that developed for these cells in other laboratories [15] for inducing MDR1 type of ABC transporters. The AA8/Emt[R1] cell lines were maintained as a monolayer in -minimal essential medium containing 5% fetal calf serum, 2 mM glutamine, 100 units/ml penicillin G, and 100 μg/ml streptomycin sulphate. The Emt[R1] cell medium also included 1 μM of emetine. The MCF-7/MCF-7MX and MDA-MB-231/MDA-MB-231Dox cell lines were maintained under monolayer conditions in DMEM containing 10% fetal calf serum, 2 mM glutamine, 100 units/ml penicillin G, and 100 μg/ml streptomycin sulphate. The MCF-7/Mx cell medium also included 250 nM of mitoxantrone and the MDA-MB-231/Dox cells medium also included 0.1 μM of doxorubicin.

All cells were kept in a 5% CO_2 incubator at 37°C. Exponentially growing cells were passaged twice a week using a standard trypsinization procedure.

Cytotoxicity assay

The level of resistance to doxorubicin and paclitaxel was determined by means of the XTT assay as previously described [8,9]. Briefly, 2×10^4 cells/well were plated in 24-well plate (NUNC), incubated without drugs for 24 h and then the initial number of cells, OD_0, was determined following incubation of with the XTT reagent using ELISA Reader (TECAN Sunrise, USA). The medium was then exchanged with ones containing different drug concentrations, 4 wells for each drug concentration (doxorubicin: 0.001-100 μM; paclitaxel: 0.0001-100 μM). After 72 h, the culture media was discharged, XTT reagent was added and the final cell number, $OD_{72\,h}$, was determined. Data obtained from 3 - 5 experiments were collected and the mean values and standard deviations (SEM) of $OD_{72\,h}$, representing final number of viable cells, were calculated for each drug concentration. Cell survival was presented as percentage of viable cells as compared to the corresponding viable cell number in no - drug controls. Drug concentrations inhibiting cell growth by 50% (IC_{50}) were calculated from relative survival curves using the median-effect principle [16].

Exposure to TTFields

As previously described [9,11], two pairs of electrodes, insulated by a ceramic having a very high dielectric constant (NovoCure Ltd, Haifa, Israel), were positioned at 90° with respect to each other in both treatment and control Petri dishes. The distance between the electrodes in each

pair was 20 mm. Each pair of electrodes was alternatively connected for 250 ms to a sinusoidal waveform generator (NovoTTF, NovoCure Ltd. Haifa, Israel) that produced 1.75 V/cm, 150 kHz fields in the medium [8]. The 150 kHz frequency of TTFields was found to be effective for treatment of all cells studied.

Four different sets of conditions in each experiment were conducted for each cell line in conjunction with each chemotherapeutic agent: untreated control cells, cells treated by the chemotherapeutic agent alone, cells exposed to TTFields, and cells having a combined TTFields - Chemo exposure (8 Petri dishes for each condition). After 72 h, the culture media was discharged, XTT reagent was added and the final number of viable cells, $OD_{72\,h}$, was determined. Data obtained from 3 - 5 experiments were collected and the mean values and standard deviations (SEM) of $OD_{72\,h}$, representing final viable cell numbers were calculated for each set of conditions. Cell survival was presented as percentage of viable cells out of the corresponding viable cell number in untreated controls. Student t-test was applied to asses the significance of the differences between results obtained for each of the four conditions tested. In order to assess the extent of possible chemotherapeutic dose reduction when applied in combination with TTFields, dose reduction indexes (DRI) for each TTFields/drug combination were calculated according to [17].

The DRI for the same level of effect (DRI_m) was calculated as the ratio of the concentration of drug alone to that of the combined drug-TTFields treatment:

$DRI_m = D_{m(drug\ alone)}/D_{m(combined\ treatment)}$. The DRIs determine the magnitude of dose reduction allowed for each drug when given in combination with TTFields, as compared with the agent dose that achieves the same level of effect. DRI values larger than 1 indicate increased sensitivity to the drug.

Intracellular Doxorubicin Accumulation

The intracellular accumulation of doxorubicin was determined for both wild type and drug resistant sub-lines. Cells were grown in total 16 Petri dishes (35 mm, NUNC) as monolayers for 24 h in drug-free medium and then incubated for 1 h in the absence or presence of doxorubicin with or without exposure to TTFields (1.75 V/cm, 150 kHz) (4 Petri dishes for each treatment condition). The cells were washed with ice cold PBS three times and solubilised with 100 μl of 2% SDS. The solutions were then transferred to black 96-well plates (NUNC) and doxorubicin fluorescence was measured by spectrofluorometry (ELISA Reader TECAN F-200) at λ_{em} 600 nm and λ_{ex} 450 nm. Data obtained from 2 - 4 experiments were collected and the mean values and standard deviations (SEM) of doxorubicin fluorescence were calculated for each condition. Student t-test was applied to asses the significance of the differences between results obtained for each of the three cell pairs.

Results

Effect of TTFields on wild type cells and their MDR sub-lines

In order to study the TTFields effect, field intensities that reduce the WT cell survival by about 50% were used. A comparison between the survival of wild type and MDR cells, when exposed to such TTFields, is given in Figure 1. The reduction in the number of viable cells is seen to be very similar (48-61% of control) in all wild type and paired MDR lines. In other words, the drug resistant cell lines have about the same sensitivity to TTFields as their corresponding wild type cell lines.

Exposure to doxorubicin or paclitaxel in combination with TTFields

Figure 2 compares between the cytotoxicity-dose curves of chemotherapeutic agents (paclitaxel and doxorubicin) of wild type cells and MDR sub-lines. It is seen that the resistivity of the MDR sub-lines is manifested in a significant right shift of the drug cytotoxicity-dose curves. As a result of these shifts the calculated IC_{50} values (Table 1) for doxorubicin and paclitaxel, for all pairs of WT-MDR cell lines studied, give very high IC_{50} ratios (resistance index RI); 55 – 79 for doxorubicin and 128 - 663 for paclitaxel.

A comparison between cell viability following separate and combined TTFields/drug exposures are presented in Figure 3. It is seen that in all combined exposures cell survival is lower as compared with exposure to any of the

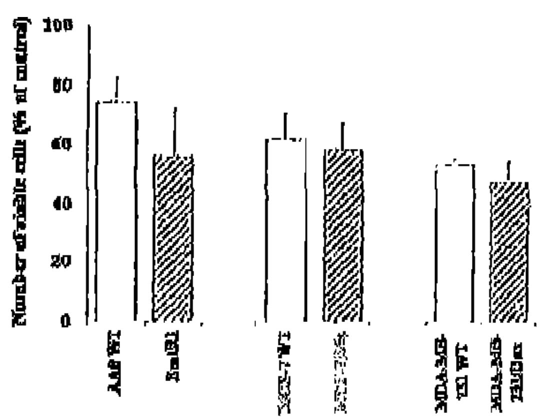

Figure 1 The reduction in the number of viable WT and MDR cells following a 72 h exposure to TTFields. Open bars - WT cells; filled bars - MDR cell sub-lines. TTFields intensity - 1.75 V/cm. Data presented as mean ± SEM of 30-36 replicate measurements from 4-5 experiments. Note that there is no statistical difference between WT and MDR pairs (student t-test).

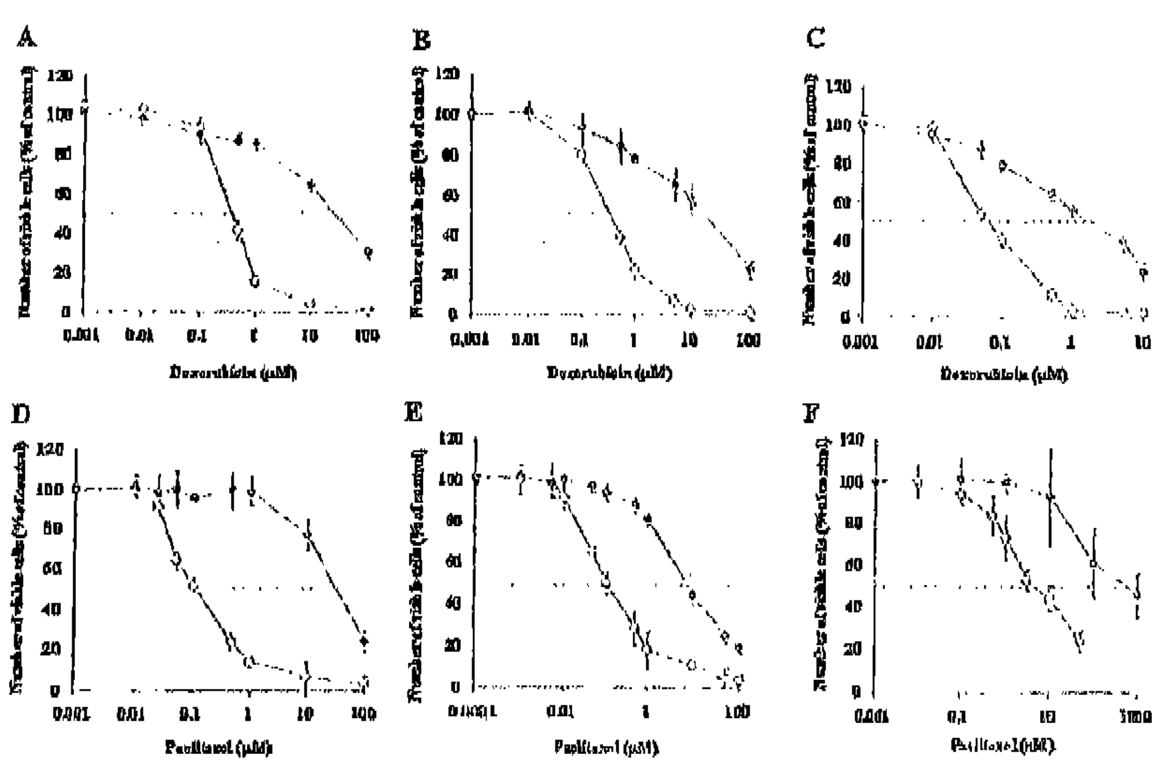

Figure 2 Cytotoxicity of doxorubicin and of paclitaxel for wild type cells and the corresponding MDR sub-line cells. A, B & C - doxorubicin. D, E & F - paclitaxel. A & D - AA8 & Emt[R1] cell lines; B & E - MCF-7 & MCF-7/Mx cell lines; C & F - MDA-MB-231 & MDA-MB-231/Dox cell lines. Open symbols - wild type cell lines, Filled symbols - MDR cell sub-lines. Treatment duration - 72 h. Data presented as mean ± SEM of 12-20 replicate measurements from 3-5 experiments.

chemical agents (doxorubicin or paclitaxel) or TTFields alone (see Figure 1). Moreover, the cell survival of the MDR sub-lines and WT cell lines, when subjected to the combined exposure is similar, i.e. the resistivity or reduced drug sensitivity of MDR cells are not evident under these conditions.

Table 2 summarizes the combined treatment efficacy for MDR cells (see Figures 2 &3) expressed in terms of Dose Reduction Index (DRI). TTFields are seen to increase the sensitivity to doxorubicin of all three MDR sub-lines by at least two orders of magnitude. The corresponding increase for paclitaxel is even greater, i.e. two to three orders of magnitude. In other words, the efficacy of combined drug/TTFields treatment of MDR cells greatly exceeds that of treatment with drug alone.

Intracellular Doxorubicin Accumulation

An inherent feature of overexpressed ABC transporters phenotype is the reduction in cell uptake of doxorubicin due to its exclusion [18]. The ability of MDR cells to exclude doxorubicin was determined by means of spectrofluorometric analysis. Figure 4A illustrates the intrac-

Table 1: IC_{50} values for doxorubicin and paclitaxel

	IC50					
Drug	AA8	EmtR1	MCF-7	MCF-7/Mx	MDA-MB-231	MDA-MB-231/Dox
Doxorubicin (μM)	0.6	48.4	0.5	30.5	0.04	2.2
Paclitaxel (μM)	0.1	65.3	0.09	9.9	0.005	0.829

Drug concentrations inhibiting cell growth by 50% (IC_{50}) were calculated from relative survival curves (see Figure 2) using the median-effect principle [16].

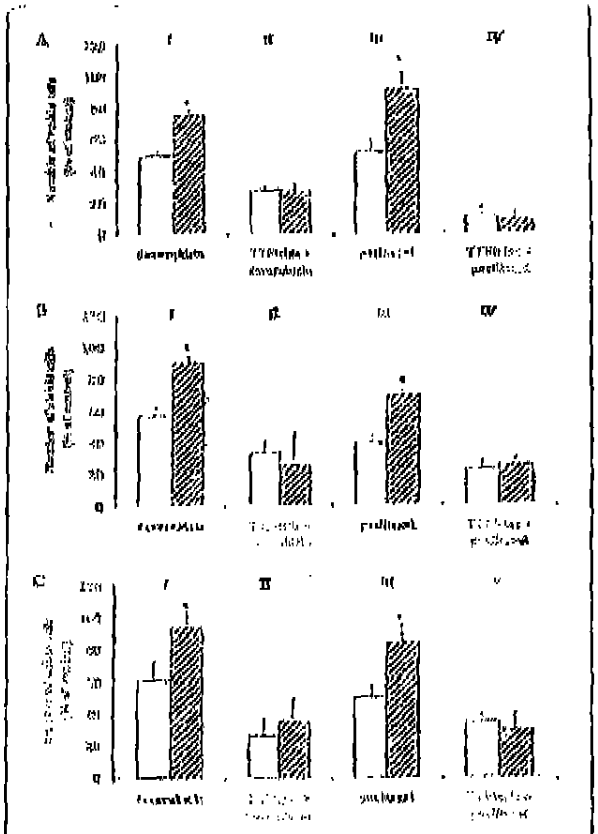

Figure 3 Effects of doxorubicin and paclitaxel when applied separately and in combination with TTFields on the viability of wild type and MDR cells. A - MDA-MB-231 & MDA-MB-231/Dox; B - MCF-7 & MCF-7/Mx; C - AA8 & Emt^{R1}. Open bars - wild type cells; filled bars - MDR cell sub-lines. I & II - Separate exposures, III & IV - combined exposures. TTFields intensity - 1.75 V/cm. Doxorubicin concentrations: A - 0.04 μM; B - 0.5 μM; C - 0.6 μM. Paclitaxel concentrations: A - 5 nM; B - 0.1 μM; C - 0.1 μM. Treatment duration - 72 h. Data presented as mean ± SEM of 24-30 replicate measurements from 3-5 experiments * $P < 0.01$, students t-test.

ellular concentration of doxorubicin in AA8 (WT) and Emt^{R1} (MDR) cell lines as a function of extracellular doxorubicin concentration with and without exposure to TTFields. As the drug is partially excluded from drug resistant sub line, the relative intracellular doxorubicin concentration in Emt^{R1} cells is lower by 44.9, 49.7 and 49.8% at 15, 30 and 45 μM extracellular doxorubicin concentration respectively, as compared with the wild type cells (Figure 4A, open symbols). Exposure of AA8 (WT) and Emt^{R1} (MDR) cell lines to TTFields during incubation with doxorubicin had no effect on the intracellular concentration of the drug in both wild type and drug resistant sub lines indicating that TTFields affect neither doxorubicin uptake nor its exclusion (Figure 4A, filled symbols). Figure 4B depicts doxorubicin accumulation by MDR sub lines relative to the corresponding WT cell

Table 2: Dose reduction indexes for MDR cell sub-lines treated alone and in combination with TTFields.

	Dose reduction index (DRI)		
Drug	EmtR1	MCF-7/Mx	MDA-MB-231/Dox
Doxorubicin	105	195	250
Paclitaxel	615	4404	> 10,000

The DRI estimates the extent to which the dose of one or more agents in the combination can be reduced to achieve effect levels that are comparable with those achieved with single agents. The effect of TTFields/drug combined treatment for each MDR cell sub-line was as shown in Figure 3. The same effect of single drug was obtained from dose-response curves (see Figure 2). The DRI was calculated as a ratio of drug concentrations used alone vs. drug concentrations used in combination with TTFields.

lines exposed to 30 μM of doxorubicin with and without TTFields. The relative intracellular doxorubicin concentration is lower by 49.7 ± 5% for Emt^{R1}, 66.4 ± 5% for MCF-7/Mx and by 32.6 ± 6% for MDA-MB-231/Dox as compared with the corresponding wild type cells (Figure 4B, open bars). TTFields have no effect on intracellular doxorubicin concentrations in all wild type and drug resistant cell lines (Figure 4B, filled bars).

Discussion

ABC transporters provide vital protection from foreign compounds by exporting these compounds from the cell, thus lowering their intracellular concentration. Unfortunately, exposure of cancer cells to chemotherapeutics, mainly during relapse treatment, causes transporter upregulation such that the resulting over-expression of ABC transporters becomes one of the main causes of treatment failure. Moreover, various tumors such as renal cell, adrenocortical, colon and hepatocellular cancers express ABCB1 and are practically chemoresistant [19]. To overcome this problem chemosensitizers that block ABC transporter-mediated efflux were developed and have been used to combat MDR. However, this approach has not been clinically successful and therefore novel approaches that bypass, rather than block ABC transporters, are being sought for [20]. As the TTFields do not affect drug transport (see Figure 4) they fall into this category.

The results of this study clearly indicate that both the MDR and WT cells are similarly sensitive to TTFields. Moreover, TTFields were shown to enhance MDR cell sensitivity to chemotherapeutic agents, so as to equal that of WT cells under the same set of conditions (Figure 3). This phenomenon can only be partially explained on the basis of the corresponding dose - response curves (Figure 2) and the drug export rate (Figure 4). As demonstrated

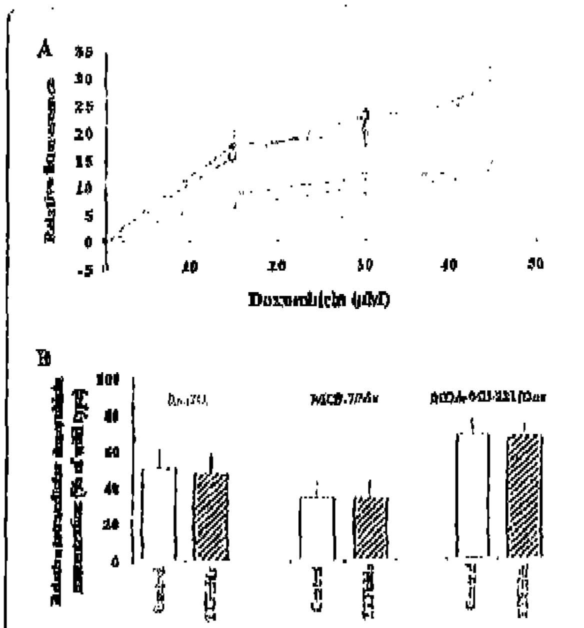

Figure 4 Effect of TTFields on doxorubicin accumulation. A - Dose response curve for AAB cells and for their MDR sub-line Emt[R]. Open symbols - cells exposed to drug alone; filled symbols - cells exposed simultaneously to drug and TTFields. Circles - AAB cell line; squares - Emt[R] sub line. Intensity of TTFields - 1.75 V/cm, frequency - 150 kHz. Treatment duration - 1 h. Data presented as means ± SEM of 16-24 replicate measurements from 2-8 experiments. B - Effect of TTFields on doxorubicin accumulation by different MDR cell sub-lines relative to their parental wild type cell lines. Ordinate: relative intracellular doxorubicin concentration in the drug resistant sub lines presented as % of the corresponding concentration in the wild type cells. Open bars - cells exposed to drug alone; filled bars - cells exposed simultaneously to drug and TTFields. Doxorubicin concentration: 30 μM. TTFields intensity - 1.75 V/cm, TTFields frequency - 150 kHz. Treatment duration - 1 h. Data are presented as mean ± SEM of 12-24 replicate measurements from 3-4 experiments

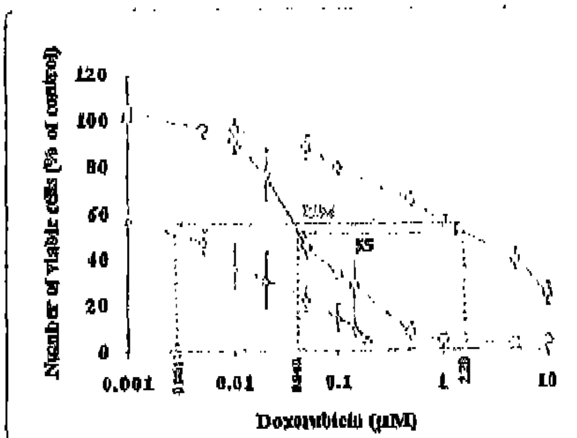

Figure 5 Effect of 72 h application of TTFields and chemotherapeutic agents, separately and in combination on the viability of MDA-MB-231 wild type cells and MDA-MB-231/Dox MDR cells. - O- MDA-MB-231 cells treated with doxorubicin alone; - Δ - MDA-MB-231 cells treated with doxorubicin in combination with TTFields (ref. [9]); - □ - MDA-MB-231/Dox cells treated with doxorubicin alone.

In Figure 5, the dose - response curve of the drug resistant cells is shifted to the right relative to the WT cells (see also Figure 2). The magnitude of the shift is such that the 50% inhibition of WT cells that is obtained at a concentration of 0.04 μM requires a concentration of 2.2 μM for the MDR sub-line, i.e. a 55 fold higher concentration. However, the data depicted in Figure 4 and corresponding reports for low doxorubicin doses [21] indicate that the drug export lowers the intracellular concentration only by a factor of about 2. This means that some other factors must be responsible for the MDR resistance that corresponds to additional 20-30 fold drug concentration change. From the data in Figure 3A we also learn that both the MDR and WT cells are similarly highly sensitive to combined chemotherapy - TTFields treatments. Thus, while a 50% inhibition of MDR cells by doxorubicin alone requires a concentration of 2.2 μM, the combined treatment of TTFields and low concentration of doxorubicin (0.0017 μM) is sufficient to induce a similar inhibition. This is equivalent to an increased intracellular concentration of doxorubicin by a factor of over 1000. Thus, TTFields seem to have effects specific to MDR cells, not related to drug transport, that increase the MDR cell's sensitivity to chemotherapy. This conclusion is consistent with that of others [22-24] that attribute the MDR resistance, in addition to reduced drug uptake, to a number of potential mechanisms such as: sugar metabolism and energy production, alterations in cytoskeletal elements, microtubule and mitochondria distribution, etc. Within the framework of the above suggested mechanisms [22-24] it seems that the integrity of cytoskeleton and microtubule as well as the mitochondria distribution may be the most vulnerable to the forces produced by TTFields. The former may be disrupted by particle movements induced by the dielectrophoresis induced during TTFields application [8] while the latter are highly polar in themselves and are therefore directly subjected to the alternating field forces.

Conclusions

The results of this study support the notion that TTFields may be used, both as an effective stand alone anti-proliferation agent for MDR cells, as well as an effective adjuvant that enhances chemotherapy efficacy. Furthermore, since TTFields are a physical modality, their therapeutic efficacy is independent of interaction with cell receptors. Therefore their efficacy is not expected to be limited to a specific set of cell types [8-12]. On the basis of the above, we believe that there is a high probability that TTFields

may prove to be an effective therapeutic modality to a wide range of human cancers including those that developed multi drug resistance.

List of abbreviations

MDR: multidrug resistance; TTFields: tumor treating electric fields; DRI: dose reduction index; WT: wild type.

Competing interests

RSS, ES and GK are employees of NovoCure Ltd. YP has a minority holding in NovoCure Ltd.

Authors' contributions

YP - Conceived the concept of TTFields, designed experiments, was involved in data analysis & interpretation of results and wrote the majority of the manuscript. RSS - Participated in experimental design, supervised the experiments execution, analyzed results and wrote parts of the manuscript. ES - Carried out the experiments. EDK - Participated in experimental design and in the interpretation of the results.
All authors read and approved the final manuscript.

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RSS, ES and GK are employees of NovoCure Ltd. YP is a consultant of NovoCure Ltd.
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Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields)

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Abstract

Background: The present study explores the efficacy and toxicity of combining a new, non-toxic, cancer treatment modality, termed Tumor Treating Fields (TTFields), with chemotherapeutic treatment in-vitro, in-vivo and in a pilot clinical trial.

Methods: Cell proliferation in culture was studied in human breast carcinoma (MDA-MB-231) and human glioma (U-118) cell lines, exposed to TTFields, paclitaxel, doxorubicin, cyclophosphamide and dacarbazine (DTIC) separately and in combinations. In addition, we studied the effects of combining chemotherapy with TTFields in an animal tumor model and in a pilot clinical trial in recurrent and newly diagnosed GBM patients.

Results: The efficacy of TTFields-chemotherapy combination in-vitro was found to be additive with a tendency towards synergism for all drugs and cell lines tested (combination index ≤ 1). The sensitivity to chemotherapeutic treatment was increased by 1–3 orders of magnitude by adjuvant TTFields therapy (dose reduction indexes 23 – 1316). Similar findings were seen in an animal tumor model. Finally, 20 GBM patients were treated with TTFields for a median duration of 1 year. No TTFields related systemic toxicity was observed in any of these patients, nor was an increase in Temozolomide toxicity seen in patients receiving combined treatment. In newly diagnosed GBM patients, combining TTFields with Temozolomide treatment led to a progression free survival of 155 weeks and overall survival of 39+ months.

Conclusion: These results indicate that combining chemotherapeutic cancer treatment with TTFields may increase chemotherapeutic efficacy and sensitivity without increasing treatment related toxicity.

Background

A new physical cancer treatment modality termed Tumor Treating Fields, or TTFields, has recently been demonstrated to be highly effective when applied to cell cultures, animal cancer models, as well as to patients suffering from locally advanced and or metastatic solid tumors [1-3]. In a pilot clinical trial, the medians of time to disease progression and overall survival of recurrent GBM patients treated by TTFields alone were more than double the reported medians of historical control patients [1]. In contrast to the widely used physical treatment modality, ionizing radiation, TTFields are not associated with significant side effects.

TTFields are low intensity (1–2 V/cm), intermediate frequency (100 – 200 kHz) alternating electric fields generated by special insulated electrodes applied to the skin surface. These specially tuned fields have no effect on quiescent cells while having an anti-mitotic effect on dividing cells. During cytokinesis, TTFields generate non-uniform intracellular fields that exert forces that move polar macromolecules and organelles towards the narrow neck, separating the newly forming daughter cells, by a process termed dielectrophoresis. These molecular and organelle movements, together with an interference with the spindle tubulin polymerization process, inhibit cell division and lead to cell death[2]. Fortunately, the dividing cells of the hematopoietic system are not affected by TTFields as the muscles surrounding the marrow containing bones serve as an effective electric field shield. Moreover, due to their relatively high frequency range and very low intensity, TTFields do not stimulate nerves and muscles, do not generate meaningful temperature elevation or puncture the cell membrane (as the strong electroporation fields do [4]). Thus, TTFields are not associated with meaningful toxicity in contrast to most anti-cancer agents currently in use [5].

In view of the unfavorable therapeutic indexes of the available effective chemical and physical (i.e. ionizing radiation) therapeutic agents, many cancer treatment protocols require simultaneous or sequential use of a number of therapeutic agents in an attempt to increase efficacy while maintaining tolerable toxicity [5-7]. Within this framework it is generally accepted that by adding ionizing radiation [8] to chemotherapy one gets both the benefit of the radiation effect as well as sensitization leading to an increased efficacy without a corresponding increase in toxicity. On the basis of the above this study explores the potential use of the new physical treatment modality, TTFields, in combination with chemotherapeutic agents in cell cultures, an animal tumor model, as well as in patients with glioblastoma (GBM). As TTFields are not associated with systemic toxicity [1] the expectation is that their addition will result in an increase in efficacy alone.

Methods

Cell cultures

Cells were cultured and maintained as previously described [1,2]. In brief: Human breast cancer (MDA-MB-231) and human glioma (U-118) obtained from ATCC (USA) were cultured in DMEM + 10% FCS media in a 5% CO_2 incubator at 37°C. Drops consisting of 200 μl suspension of cells (100 × 10^3 cells/ml) were placed at the centre of 35 mm Petri dishes, incubated for 2 hours to allow for cell attachment, then 1.5 ml of media were added and incubation was continued for an additional 22 h. Following this, the baseline cell count was estimated using the XTT colorimetric method (expressed as OD_0). The media in the Petri dishes was replaced by fresh media (3 ml), with or without a chemotherapeutic agent and incubated at a final temperature of 37° ± 0.5°C for 24 to 72 hours after which the cell number was re-estimated (OD_1). The relative number of viable cells at each time point following baseline was expressed as OD_1/OD_0 and treatment efficacy as the % change in proliferation relative to control:

$$(OD_1/OD_0)_{experiment} * 100/(OD_1/OD_0)_{control} \qquad (1)$$

TTFields treatment of cultures

As previously described [1,2], two pairs of electrodes, insulated by a high dielectric constant ceramic, were positioned normal to each other at a distance of 20 mm in treatment and control dishes. In the former, the electrodes were connected to sinusoidal waveform generator that generated fields of optimal frequencies in the medium [1,2,9]: 150 kHz for breast cancer and 200 kHz for glioma, that changed direction by 90° every 250 ms. Field intensity was measured as described previously [2] and expressed as V/cm. For 72 h experiments the TTFields intensity of 1.75 V/cm was used. For 24 h experiments 0.65, 1.25 and 1.75 V/cm TTFields were used.

Four different sets of experiments were conducted in conjunction with each chemotherapeutic agent: untreated sham control, treatment with TTFields, treatment with the chemotherapeutic agents, and combined TTFields – Chemo treatment.

Assessment of combination index and dose reduction index

The Chou and Talalay [10] method for assessing the combined effect of multiple drugs was used for the drug – TTFields combinations. In order to assess whether the interactions between TTFields and each of the chemotherapeutic agents is synergistic, additive or antagonistic, combination indexes were calculated as follows: TTFields intensity replaced the concentration (dose) variable in the analyses. Dose-response curves were generated for TTFields and each drug to determine the median effect

points. Variable ratios of drug concentrations to TTFields intensities were used to calculate the Combination Indexes (CI) as follows:

$$CI = (C_{Drug(in combination), X\% effect}/C_{Drug(alone), X\% effect}) + (I_{TTFields(in combination), X\% effect}/I_{TTFields(alone), X\% effect}) \quad (2)$$

Where: C are the drug concentrations and I the TTFields intensities use to achieve a preset X% effect. Relationships of CI<1 indicate more than additive – synergy, CI = 1 reflects additivity – summation and CI>1 indicates less than additive or antagonism.

In order to asses whether TTFields increase the sensitivity of tumor cells to various chemotherapeutic agents, the dose reduction index (DRI) of for each of these agents was calculated according to [11]. In short, the median-effect plots were for each chemotherapy-TTFields combination, were constructed. The ratio of affected to unaffected number of cells (f_a/f_u) was plotted versus drug concentration on a log-log scale. The median effect point (D_m) was assessed by deriving the slope of the linear regression for each of the plots. The DRI for a 50% effect (DRI_m) was calculated as the ratio of D_m for drug alone and for combined drug-TTFields:

$$DRI_m = D_{m(drugalone)}/D_{m(combinedtreatment)} \quad (3)$$

A DRI greater than 1 indicates an increase in sensitivity to the drug. The greater the DRI, the more significant the possible dose reduction.

In-vivo experiments

Combined TTFields and Paclitaxel efficacy study in VX2 tumor bearing rabbits was conducted after approval by the NovoCure Internal Animal Care and Use Committee. All painful or anxiogenic procedures were performed under general anesthesia induced by intramuscular administration of 30 mg/kg of ketamine hydrochloride, 10 mg/kg xylazine hydrochloride and 1.5 mg/kg Acepromazine. The tumor tissue required for implantation was obtained from VX-2 tumor bearing carrier rabbits. The carrier rabbits had VX-2 tumors implanted intramuscularly in the thigh. When the tumor reached approximately 1 cm in diameter (about 3 weeks from implantation), the tumor was excised, minced in sterile saline and VX-2 tumor fragments obtained. Two fragments were injected using a large bore needle into the thigh muscles of both legs in a recipient rabbit for tumor propagation. For experimental animals, after laparotomy, a fragment of tumor tissue (1 mm^3) was implanted beneath the kidney capsule of the recipient rabbit.

The current experiment comprised 28 animals (7 in each of 4 groups). Fourteen days after tumor implantation the initial tumor volume was assessed based on serial (2.2 mm interval) T1 weighted axial MRI images (1.5 Tesla, GE Genesis-Signa) obtained 3 minutes following IV injection of 3 ml of Gadolinium. Tumor volume was assessed from the area of the contrast enhancing lesion in each section. The animals were assigned randomly into 4 groups before treatment start:

1. TTFields treated group: TTFields were applied by using the NovoTTF-100A device (NovoCure LTD., Haifa, Israel). An optimal frequency of 150 kHz and intensity of 1–2 V/cm were used. TTFields were switched sequentially between two perpendicular field directions.

2. Control group: sham electrode heated to mimic heat generated by the TTFields treatment. (38–39.9°C)

3. Paclitaxel (Medixel Injection., Taro Pharmaceutical Industries LTD., Israel) treated group: 3 mg/animal diluted in 100 ml of normal saline were infused intravenously over a period of 30 minutes. Premedication was given subcutaneous 8 hours before and immediately prior to Paclitaxel administration (Dexamethasone (Dexaveto-0.2 veterinary, V.M.D n.v/s.a Belgium) 0.5 mg/animal; Pramine (Metoclopramide HCL, Rafa Laboratories LTD., Israel) 1 mg/animal; Diphenhydramine (10%, Medical M., Israel) 10 mg/animal).

4. Combined TTFields and Paclitaxel treatment as above.

TTFields were delivered to awake and behaving rabbits through four insulated electrode arrays placed circumferentially around the animal's abdomen, caudal to the rib-cage. The electrode insulation consisted of a high dielectric constant (>10,000) ceramic (PMN-PT) allowing efficient energy transfer through the insulation into the animals body at the given frequencies. The electrodes were connected by a spiral cable to a swivel mechanism at the top of the cage, enabling the free movement. TTFields were generated using the NovoTTF-100A system (NovoCure Ltd., Haifa, Israel). The animals were treated for 21 days continuously with MRI performed on days 14 and 21 for tumor volume assessment. The TTFields intensity within the kidneys of the rabbits, using this electrode configuration, is between 1–3 V/cm (based on both finite element mesh simulations and direct measurements using an invasive probe – data not shown).

Pilot clinical trial

A single arm, pilot trial of the safety and efficacy of TTFields treatment was performed in 20 patients with histologically proven glioblastoma multiforme (GBM) that met the inclusion/exclusion criteria specified in Supplemental Material Appendix A (briefly, KPS 70–100%, Age ≥ 18). The trial was performed according to a protocol

approved by the Na Homolce Institutional Review Board and the Czech Republic Ministry of Health. The patients were divided into two groups: The first group included 10 patients with recurrent GBM treated with TTFields alone following failure of maintenance Temozolomide [1]. The second group consisted of 10 newly diagnosed patients who were at least 4 weeks post radiation therapy, who received TTFields combined with maintenance Temozolomide. Prior to initiation of treatment, all patients underwent a baseline contrast MRI of the head, chest radiograph, EEG, ECG, complete blood & urine analyses, physical examination and neurological status. The patients were hospitalized for 1–3 days for observation and then released home where they received multiple 4-week courses of continuous NovoTTF-100A treatment until progression. The patients were seen once/month at an outpatient clinic where they underwent an examination similar to the initial one. TTFields were applied to the patients using the NovoTTF-100A device set to deliver 200 kHz, 0.7 V/cm (RMS) fields (at the center of the brain) in 2 perpendicular directions, 1 second in each direction sequentially. The TTFields were applied continuously using four insulated electrode arrays, each having a surface area of 22.5 cm^2, placed on opposing sides of the head with the tumor positioned directly between the electrode pairs [1]. As previously reported, to avoid electrolysis at the electrode surface and intracellular ion concentration changes that accompany long term current application, the electrodes were completely insulated by a ceramic having a very high dielectric constant (>10,000) that allowed the generation of the necessary electric fields [1,2]. Using this electrode configuration, the lowest TTFields intensity at the center of the brain was 0.7 V/cm (RMS). This intensity was calculated using finite element mesh simulations and verified by direct measurement in large animals and a human volunteer [1].

The outcome endpoints of the study included safety, overall survival (OS) and progression free survival (PFS). Assessment of tumor response was based on monthly MRIs according to the Macdonald criteria [12]. Median OS and PFS were determined using Kaplan Meier curves [13]. In the first group, PFS in NovoTTF-100A treated patients was compared to a matched group of concurrent control patients who received salvage chemotherapy at recurrence (n = 18). PFS in Temozolomide/NovoTTF-100A treated patients was compared to the PFS of a matched group of concurrent control patients (n = 32) who received Temozolomide alone (according to the protocol described by Stupp et al. [14]). OS in both groups was compared to matched historical control data with the same Karnofsky performance score (>60) and age [14].

Results

Breast cancer cell cultures

Dose – response of culture exposure to TTFields, paclitaxel, doxorubicin and cyclophosphamide, alone and in combination

The relationship between TTFields intensity, at 150 kHz, and cell proliferation rate is given in Figure 1A. At the lowest field intensity of 0.63 V/cm there is no significant change in cell proliferation. For TTFields intensities of 1.25, 1.75 and 2.95 V/cm cell proliferation decreases (control = 100%) to: 90 ± 3%, 74 ± 4% and 25 ± 5%, respectively. The dose-response curves of cells exposed to paclitaxel, doxorubicin and cyclophosphamide, alone and in combination with 1.75 V/cm TTFields for 72 hours, are given in Figures 1B, C & D. For each drug alone there is a decrease in cell proliferation with increase in concentration. For cyclophosphamide and doxorubicin complete inhibition of proliferation is achieved at high drug concentrations. For paclitaxel, the inhibitory effect of the drug saturates at about 300 nM, near the 13% level, indicating that a fraction of the cells are insensitive to the agent. Combined treatment with TTFields and each of the chemotherapeutic agents caused a leftward shift of the dose response curves. This shift can be expressed as a decrease in the drug concentration leading to 50% inhibition of cell proliferation (IC_{50} – Table 1).

Time course of the effects TTFields, paclitaxel, doxorubicin and cyclophosphamide

Figure 2 displays the time course of proliferation inhibition during a continuous 72 hour exposure to TTFields, paclitaxel, doxorubicin and cyclophosphamide alone and in combination with 1.75 V/cm TTFields. It is seen that in all cases the inhibition during combined exposure is greater than for the chemotherapeutic agent alone. The differences between the separate and combined effects increase with time.

Recovery from treatment

Figure 3 demonstrates that a 24 hour exposure to individual chemotherapeutic agents induces a reduction of approximately 25% in viable cell number compared to

Table 1: IC_{50} for chemotherapeutic drugs alone and in combination with 1.75 V/cm TTFields after 72 hours of continuous treatment.

Chemotherapy	IC_{50} (drug alone)	IC_{50} (drug-TTFields combination)
Paclitaxel	5.00 nM	0.005 nM
Doxorubicin	0.04 μM	0.002 μM
Cyclophosphamide	6.60 mM	0.044 mM

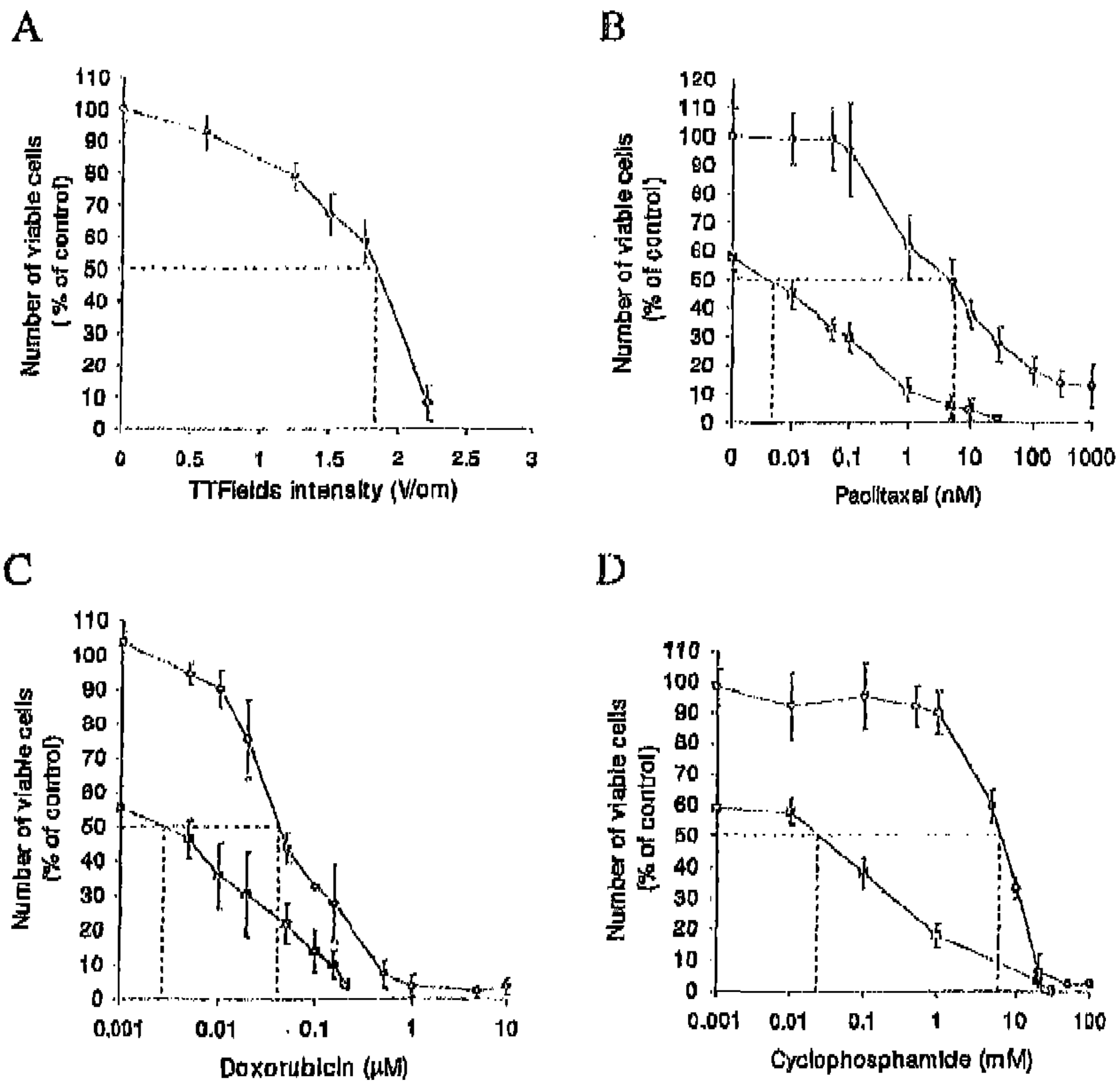

Figure 1
Effect of 72 hour continuous application of TTFields and chemotherapeutic agents, separately and in combination on the cell proliferation of ER-negative MDA-MB-231 cells (presented as percent viable cells compared to control). (A) Percent viable cells vs. TTFields intensity. Effect of different concentrations of paclitaxel (B), doxorubicin (C) and cyclophosphamide (D), alone and in combination with TTFields of 1.75 V/cm. In B, C and D Filled Circles – represent drug alone; Filled Squares – drug in combination with TTFields. Each point represents mean values ± SEM of 18 to 36 replicate measurements. Dotted lines demarcate the IC_{50} values for each curve.

controls. The proliferation rate (slope of the graph) recovers almost completely during the following 48 hours, except for doxorubicin, where recovery is slower and delayed by about 24 hours. In contrast, addition of TTFields to any one of these chemotherapeutic agents results in irreversible and complete inhibition of cell pro-

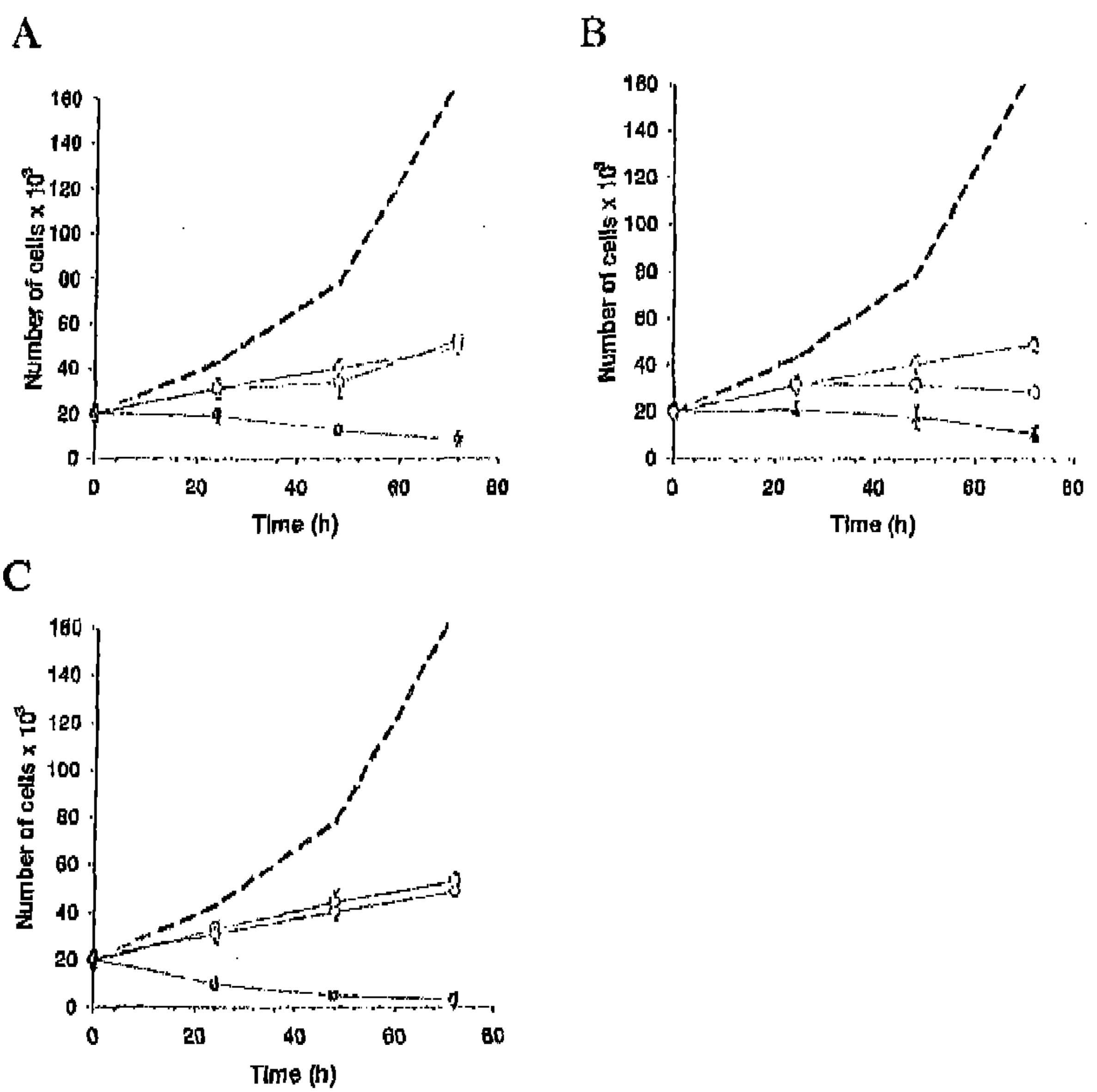

Figure 2
Time course of the effects of 72 hour exposure of MDA cells to Paclitaxel (A), Doxorubicin (B) and Cyclophosphamide (C) alone and in combination with 1.75 V/cm TTFields. Each graph shows the number of viable cells in culture over time in control cells (interrupted lines), drug alone (open squares), TTFields alone (open circles) and drug-TTFields combination (closed squares). Data are presented as mean ± SEM. Each experimental condition included 18–36 samples.

liferation rate manifested as a decrease in the number of cells in culture. For Cyclophosphamide there is an almost complete loss of viable cells after 72 hours of combined treatment.

Glioma cell cultures

Combined effect of DTIC and TTFields in human glioma cell cultures
In order to asses the combination between Temozolomide and TTFields in glioma cells, DTIC and TTFields

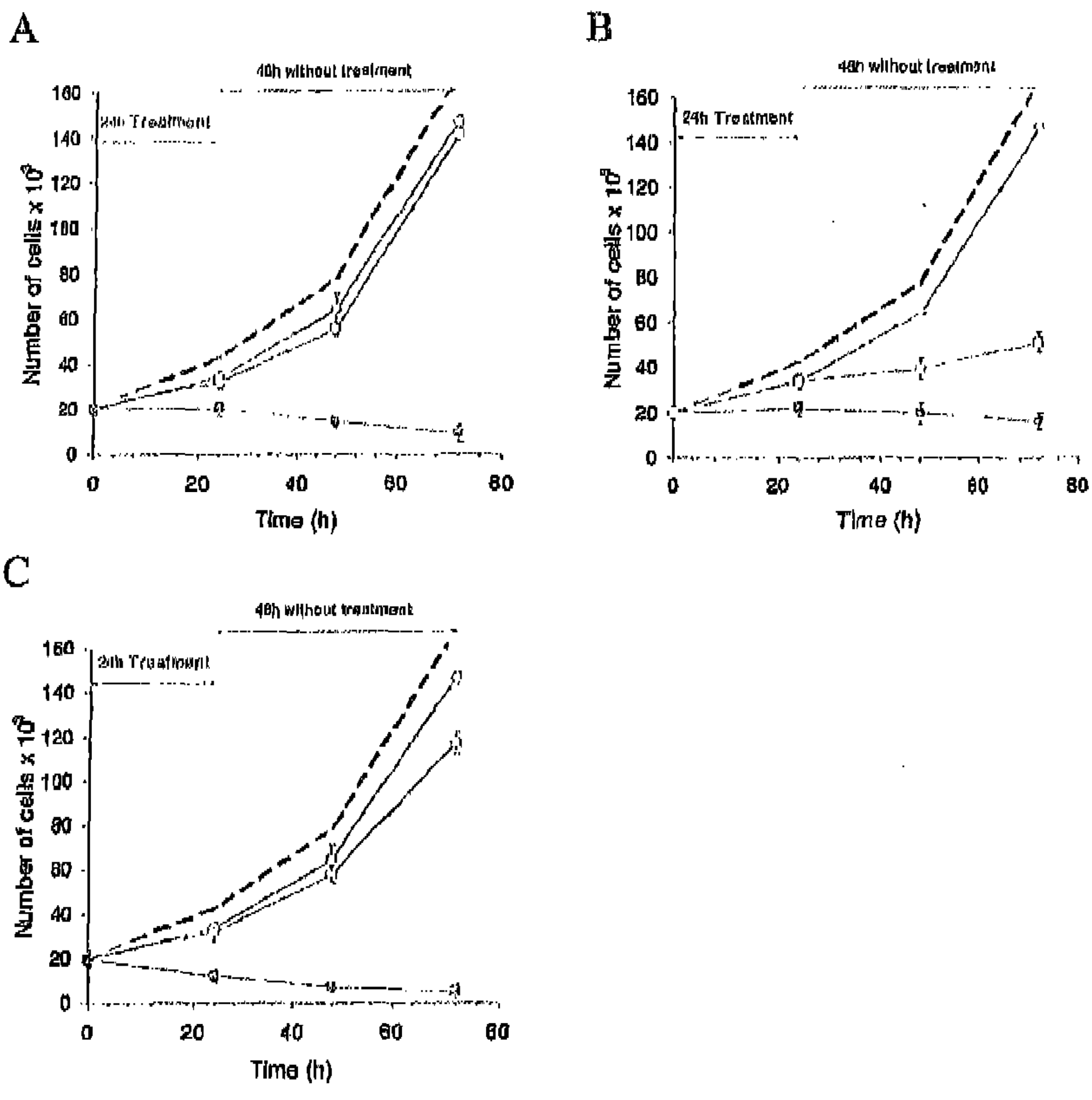

Figure 3
Time course of recovery from 24 hour exposure to Paclitaxel (A), Doxorubicin (B) and Cyclophosphamide (C) alone and in combination with 1.75 V/cm TTFields. Each graph shows the number of viable cells in culture over time in control cells (interrupted lines), drug alone (open squares), TTFields alone (open circles) and drug-TTFields combination (closed squares). Data are presented as mean ± SEM. Each experimental condition included 18–36 samples.

were applied alone and in combination to U-118 cells in culture. Both DTIC and Temozolomide act through a common degradation product (MTIC). Thus light activated DTIC was used for these experiments as described previously [15,16]. Figure 4 compares the DTIC dose-response curve, with that obtained with DTIC – TTFields combination. As we have shown in breast cancer cultures, the addition of TTFields to a chemotherapeutic agent

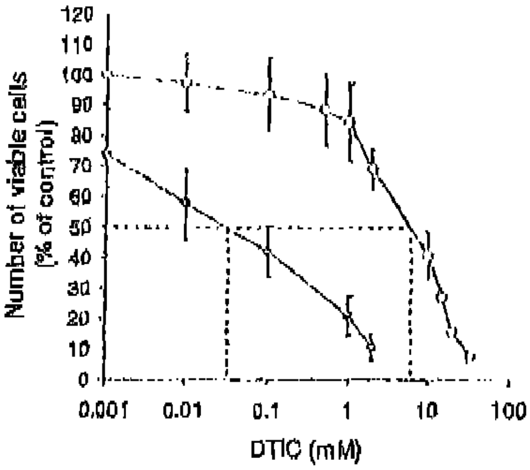

Figure 4
Effect of light activated DTIC and TTFields (1.75 V/cm) on cell proliferation of U-118 glioma cells, presented as percent of viable cells compared to control. Open Circles – 72 hours of DTIC treatment alone. Filled Circles – 72 h of Combined DTIC – TTFields treatment.

causes a leftward shift in the dose-response curve in glioma cells as well. The IC_{50} for DTIC alone in Figure 4 is 6.4 mM, whereas the IC_{50} for combined DTIC-TTFields is two orders of magnitude lower (0.023 mM).

Analysis of combination efficacy and sensitivity in-vitro
Combination indexes

The mode of interaction between TTFields and chemotherapeutic agents (synergism, additivity or antagonism) can be analysed using Combination Indexes (CI) as described by [10,17]. In order to calculate the CIs for TTFields-Chemotherapeutic agents, the extent of inhibition of cell growth was assessed after 24 hours of treatment with Paclitaxel, Doxorubicin and Cyclophosphamide alone or in combination with different intensities of TTFields (0.625–1.75 V/cm; see Materials and Methods). Table 2 demonstrates that for breast cancer cells the CI for Doxorubicin is very close to 1, indicating additivity [10,11]. In contrast, for TTFields with Paclitaxel and Cyclophosphamide the CIs are <1 indicating additivity with a tendency towards synergism.

Dose reduction indexes

In order to assess the extent of possible chemotherapeutic dose reduction when applied in combination with TTFields, dose reduction indexes (DRI) for each drug-TTFields combination were calculated based on the methodology described by [11]. The DRIs for TTFields-drug interaction after 72 hours of combined treatment was 1316 for paclitaxel, 23 for doxorubicin, 152 for cyclophosphamide and 175 for DTIC (in U-118 glioma cells). Thus a significantly reduced dose (1–3 orders of magnitude lower drug concentration) may be used in combination with TTFields to achieve the same level of efficacy.

Table 2: Calculated Combination Indexes for human breast cancer (MDA-MB-231) cells treated with paclitaxel, doxorubicin or cyclophosphamide in combination with TTFields.

	Combination Index		
	MDA-MB-231 cells		
TTFields Intensity (V/cm)	Paclitaxel	Doxorubicin	Cyclophosphamide
	CI_{40}	CI_{10}	CI_{50}
0.625	-	-	0.74
1.25	0.97	0.99	0.84
1.75	0.86	0.98	0.95

Effect of combined paclitaxel and TTFields on VX2 tumors in rabbits

Prior to testing the combined efficacy of paclitaxel and TTFields on VX2 tumors implanted within the kidneys of rabbits, the dose-response of paclitaxel in this animal tumor model was determined. A dose of Paclitaxel leading consistently to a 15–20% inhibition in tumor growth (5 mg/rabbit) was chosen for subsequent combination experiments with TTFields.

As seen in Figure 5, untreated tumors increased in volume by a factor of 70 from baseline, Paclitaxel treated tumors grew by a factor of 58 from baseline, TTFields treated tumors grew by a factor of 34 from baseline and tumors treated by TTFields-Paclitaxel combination grew by a factor of 22 from baseline. Thus the TTFields-Paclitaxel combination treatment inhibited tumor growth by 69% compared to the growth of control tumors, while Paclitaxel alone inhibited tumor growth by 15% compared to the growth of control tumors, and TTFields alone by 53% compared to the growth of control tumors. Thus, additivity was seen between TTFields and Paclitaxel at the intensity and concentration used. Differences between curves were statistically significant ($p < 0.01$; ANOVA).

Pilot clinical trial in GBM patients

Twenty patients with histological diagnosis of GBM were treated continuously for an average of 1 year (range 2.5–24 months). Ten recurrent GBM patients were treated with TTFields alone as salvage therapy. Ten newly diagnosed

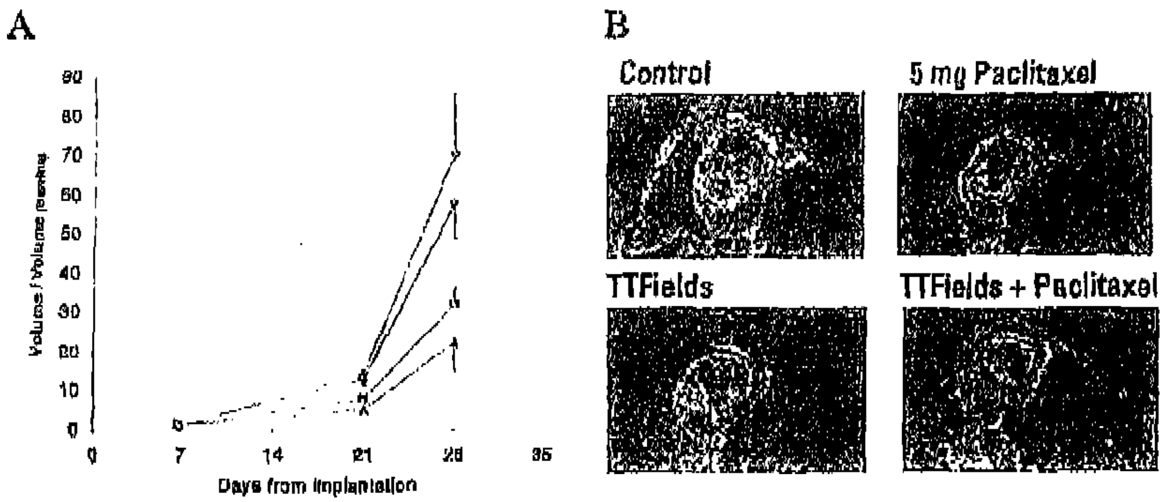

Figure 5
Effect of combined Paclitaxel/TTFields on VX2 tumors in Rabbits. A VX-2 Kidney tumor volumes were normalized to pre-treatment tumor volume (day 7) and are presented over time for: control (diamonds), 5 mg Paclitaxel (circles), TTFields (squares) and combined TTFields-Paclitaxel (triangles). The effect of combined TTFields and Paclitaxel is equal to the sum of the effects of either treatment alone at both time points measured during the study (2 and 3 weeks from treatment start; n = 23; bars are standard errors of means). B Exemplary MRIs of the maximal contrast enhancing tumor area (demarcated by orange boarders) in the kidneys of rabbits in each of the experimental groups (sham control, Paclitaxel 5 mg, TTFields 2 V/cm, combined Paclitaxel and TTFields).

GBM patients, that had undergone surgery and thereafter received radiation therapy with adjuvant Temozolomide, were treated with the combination of TTFields in parallel to maintenance Temozolomide [14]. In both groups of patients no device related serious adverse effects were observed. The only device related toxicity reported was a dermatitis which appeared most often (18 of 20 patients) during the second month of treatment. The severity of the dermatitis decreased upon use of topical corticosteroids and periodic electrode relocation. The dermatitis continued for the duration of treatment and resolved completely within days to weeks from treatment termination.

In the second group, no increase in Temozolomide related adverse events was seen due to the combination with TTFields (see Table 3).

As reported previously [1], both progression free survival (PFS) and overall survival (OS) in the recurrent GBM salvage therapy group were at least double that of concurrent and historical controls, respectively. The efficacy of the TTFields-Temozolomide combination in the second group of patients was assessed using Kaplan Meier curves [13] of PFS and OS. The Kaplan Meier curves for the PFS of these patients, treated by combined TTFields - Temozolomide are shown in Figure 6A. The median PFS of the combination treated patients is 155 weeks versus 31 weeks for concurrent controls treated with maintenance Temozolomide alone. Note that 5 of 10 patients are currently progression free. Figure 6B compares the OS of the patients that received the combination treatment (Red line) with a matched historical control (KPS>60, Median age 54) (Black line [14]). It is seen that for the TTFields - Temozolomide combination treated patients, the Median OS > 39 months versus about 14.7 months for matched historical control patients who received maintenance Temozolomide alone. It should be noted that at the time

Table 3: Toxicities by grade and causality in the newly diagnosed GBM patients treated with combined TTFields-Temozolomide.

	Grade		Causality assessment
	I-II	III-IV	
Elevated LFTs	6/10	0/10	Anti Epileptic Drugs
Hyperglycemia	4/10	0/10	Oral Steroids
Anemia	6/10	0/10	Temozolomide
Thrombocytopenia	2/10	0/10	Temozolomide
Leucopenia	3/10	0/10	Temozolomide
Headache	2/10	0/10	Underlying disease
Seizures	1/10	0/10	Underlying disease
Dermatitis	10/10	0/10	NovoTTF-100A

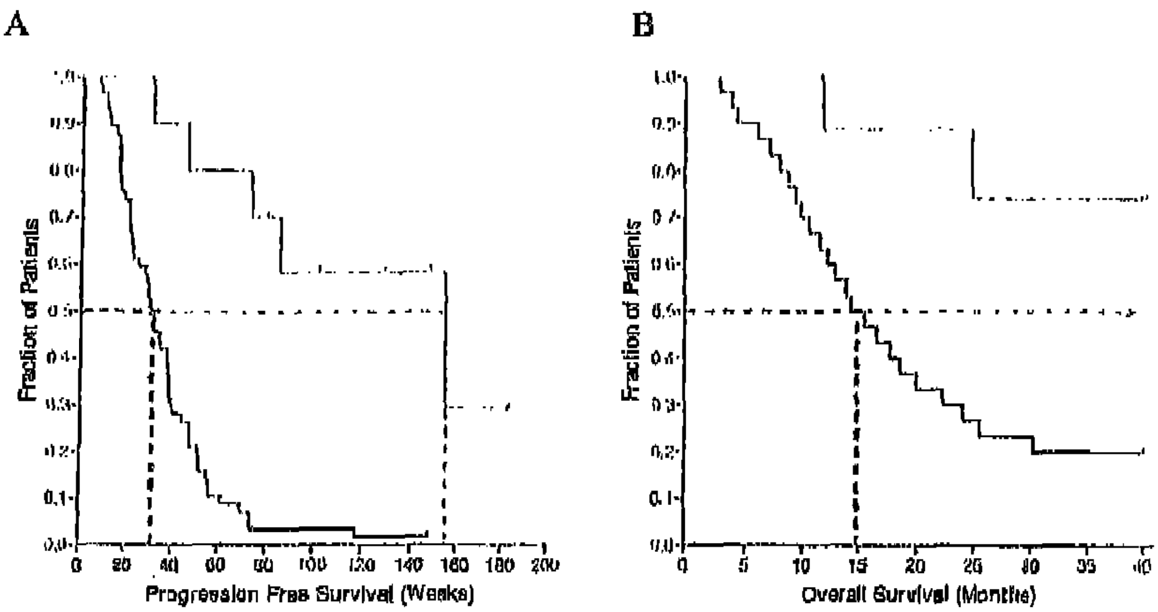

Figure 6

Kaplan Meier curves for A – progression free survival (PFS) and B – overall survival (OS) of newly diagnosed GBM patients receiving either combined TTFields – Temozolomide treatment or Temozolomide treatment alone. Red line – patients receiving combined TTFields – Temozolomide treatment (n = 10). Black line – concurrent/historical control patients that received Temozolomide treatment alone. A – The difference between the PFS curves is highly significant – Log-Rank Test (P = 0.0002), Hazard Ratio 3.32 (95%CI 1.9–5.9). B – The difference between the OS curves is highly significant – (Log-Rank Test; P = 0.0018). Dashed lines mark the median values for each curve.

of this report 8 of 10 patients, receiving the TTFields-Temozolomide combination treatment, are alive.

Discussion

Cancer treatment with drug combinations was introduced in order to improve therapeutic indexes through dose reduction of each drug and increase treatment efficacy. In this study the exposure of cancer cells to combined chemotherapy and TTFields was studied in cell cultures, an animal tumor model and in a pilot clinical trial in recurrent and newly diagnosed GBM patients. The results of this study support the possibility that TTFields may be used, not only as an effective stand alone anti-proliferation agent (as shown previously in [1]), but also as an effective adjuvant that enhances chemotherapy efficacy without an increase in toxicity. In addition to this increase in efficacy, these results raise the possibility of dose reduction of chemotherapy when used in combination with TTFields. This is of outmost importance since, at tolerable doses the efficacy of available cancer therapeutic agents is often far from optimum while being associated with a high degree of toxicity.

With regards to the mechanisms involved, one may assume that tumor cells are sensitized to TTFields by chemotherapy, much like another well established physical therapy – ionizing radiation [8,18,19]. In the specific case of Paclitaxel, one of the most commonly used treatments for late-stage human breast cancer [20], the combined effect may be attributed to their similar site of action – the spindle microtubules [1,2,21]. Taxanes act by stabilizing the link between individual tubulin dimmers [21]. As illustrated schematically in Figure 7A taxanes increase the length of tubulin filaments within the cell. One of the mechanisms of action of TTFields is the misalignment of mitotic spindle filaments as a result of TTFields forces on tubulin chains [2]. The increase in filament length due to taxanes, increases the dipole moment of these macromolecules, leading to an increase in the TTFields induced forces and thus to a higher sensitivity of the cell to TTFields (see Figure 7A).

Doxorubicin that has a broad spectrum of activity both in experimental tumor models and in human malignancy, affects both DNA and RNA synthesis [22]. Cyclophosphamide (an alkylating agent) inhibits DNA replication by

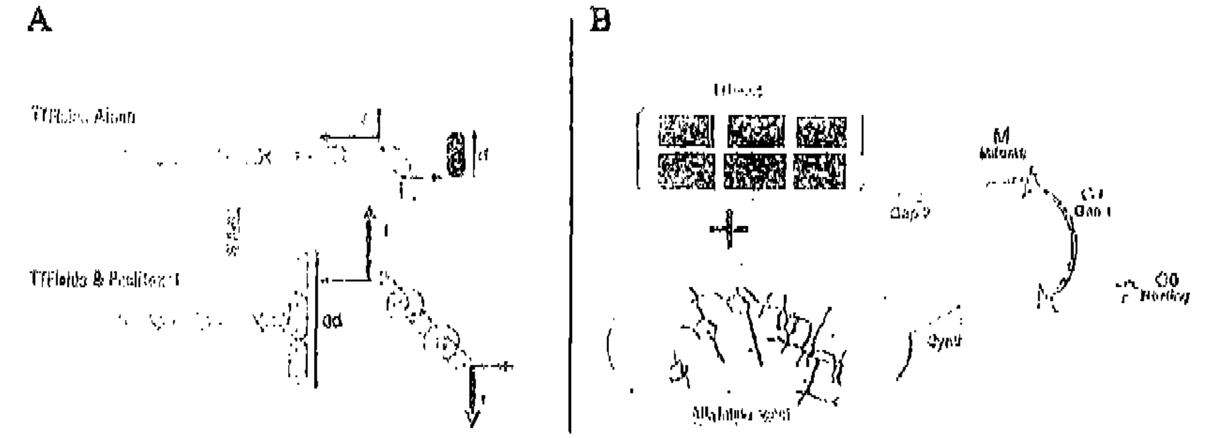

Figure 7
Mechanisms of potentiation of chemotherapeutic efficacy by TTFields. A Tubulin chains are elongated by Paclitaxel, leading to an increase in the average dipole moment of free tubulin chains (d – length of an individual tubulin dimmer; f – force between the microtubule chain and the dimmer; F-force acting on the tubulin dimmers by TTFields; Arrow length is proportional to the intensity of these forces). The forces TTFields exert on these larger dipoles, F, are enhanced leading to an increase in the disruption of the mitotic spindle by TTFields. **B** TTFields act as an M-phase inhibitor, while alkylating agents act at the G and S phases of the cell cycle. This separation between cell cycle phases affected explains the additivity seen experimentally.

interfering with the separation of the double stranded DNA essential for transcription [23]. As illustrated in Figure 7B, since TTFields act at a completely different stage (M phase) of the cell cycle from both these agents, additivity between chemotherapy and TTFields can be expected.

Since the data for newly diagnosed GBM patients, which points to well over a 300% increase in PFS and OS, was obtained only with combination treatment, one cannot directly separate the TTFields effects from the chemotherapeutic effect. However, if we assume that the TTFields therapeutic efficacy for newly diagnosed patients is similar to recurrent GBM, i.e. the median of OS is increased by 270% [1] while the published Temozolomide data indicates an increase of about 20% in OS compared to ionizing radiation treatment alone [14], the results presented in Figure 6 point towards additivity between TTFields and Temozolomide. It is important to note that this significant increase in efficacy was obtained without any increase in device or drug related toxicity (see table 3).

An additional important finding is that both 24 h and 72 h combination treatments in-vitro result in severe irreversible cellular damage in contrast to chemotherapy alone. This result strengthens the assumption that combination therapy with TTFields may be much more effective than treatment by individual agents.

Conclusion

The results of the present study support the notion that TTFields may be used clinically not only as an anti-proliferation agent as shown before [1], but also as effective sensitizers of currently used chemotherapeutic agents. Such sensitization was not shown to be associated with any additional systemic toxicity. Moreover, as demonstrated by the high DRIs calculated in this study, chemo/TTFields combinations are expected to provide the same or even greater therapeutic efficacy with much lower drug concentrations thus lowering further the overall toxicity.

Competing interests

EK, RSS, AI, DM, ZG, ES and YW are employees of NovoCure Ltd.

YP has a minority holding in NovoCure Ltd.

VD, FT, JV and DG have no competing interests.

Authors' contributions

EK – planned the pre-clinical and clinical experiments, supervised their execution, analyzed results and wrote parts of the manuscript. RSS and ET – Performed the in-vitro experiment and assisted in the in-vivo experiments. DM, ZG and AI – Performed the in-vivo experiments. DG – Performed the MRI imaging for the in-vivo experiments. YW – Planned the medical devices and treatment parame-

ters for all experiments. VD, FT and JV - performed the clinical trial in GBM patients (clinical investigators). YP - invented the concept of TTFields, helped interpret all results and wrote the majority of the manuscript.

Appendix

Appendix A – Eligibility criteria for the pilot GBM trial

Inclusion criteria:

Histologically proven diagnosis of GBM.

Age over 18 years.

Karnofsky scale ≥ 70.

Participants of child bearing age had to be receiving efficient contraception.

Willing and able to sign an informed consent prior to participation in the study.

Exclusion criteria:

Patients actively participating in another clinical trial

Patients who received any anti-tumor therapy in the four weeks prior to trial initiation (steroids are permitted; however, the dose must be stable or decreasing during the trial).

Patients suspected of suffering from radiation necrosis (according to a PET scan).

Pregnancy

Patients with one of the following co-morbidities:

Patients with an implanted pacemaker or documented arrhythmias.

Significant renal, hepatic or hematologic disease.

Significant additional neurological disorder:

Seizure disorder unrelated to the patient's tumor

Pre-existing dementia

Progressive degenerative neurological disorder

Meningitis or encephalitis

Hydrocephalus associated with increased intracranial pressure (ICP)

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Review

Expert Opinion

Tumor treating fields: concept, evidence and future

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Introduction: Local control is fundamental, both for the curative as well as the palliative treatment of cancer. Tumor treating fields (TTFields) are low intensity (1 – 2 V/cm), intermediate frequency (100 – 200 kHz) alternating electric fields administered using insulated electrodes placed on the skin surrounding the region of a malignant tumor. TTFields were shown to destroy cells within the process of mitosis via apoptosis, thereby inhibiting tumor growth. TTFields have no effect on non-dividing cells.

Areas covered: This article reviews *in vitro* and *in vivo* preclinical studies, demonstrating the activity of TTFields both as a monotherapy as well as in combination with several cytotoxic agents. Furthermore, it summarizes the clinical experience with TTFields, mainly in two indications: one in recurrent glioblastoma multiforme: in a large prospective randomized Phase III trial TTFields was compared with best standard care (including chemotherapy): TTFields significantly improved median overall survival (OS) compared with standard therapy (7.8 vs 6.1 months) for the patients treated per protocol. Importantly, quality of life was also better in the TTFields group. The second indication was a Phase II study in second-line non-small cell lung cancer, where TTFields was administered concomitantly with pemetrexed. This combination resulted in an excellent median OS of 13.8 months. Interestingly, the progression-free survival (PFS) within the area of the TTFields was 28, however, outside the TTFields the PFS was only 22 weeks.

Expert opinion: The proof of concept of TTFields has been well demonstrated in the preclinical setting, and the clinical data seem promising in various tumor types. The side effects of TTFields were minimal and in general consisted of skin reaction to the electrodes. There are a number of ways in which TTFields could be further evaluated, for example, in combination with chemotherapy, as a maintenance treatment, or as a salvage therapy if radiotherapy or surgery is not possible. While more clinical data are clearly needed, TTFields is an emerging and promising novel treatment concept.

Keywords: cancer, electric fields, glioblastoma, non-small cell lung cancer, TTFields

Expert Opin. Investig. Drugs [Early Online]

1. Background

Alternating electric fields have been used since many years for the diagnosis, research and treatment of various medical conditions. Such electric fields have different properties, depending on their frequency and intensity (Table 1). Very low frequencies (lower than 1 kHz) are used to excite the membrane of muscles and nerves, thereby leading to membrane depolarization and finally to action potentials [1,2]. Higher frequency alternating electric fields penetrate cells better, but the overall effect of hyper-depolarization on the cell membrane polarities in a way that the integrated stimulation does not yield an action potential. However, at frequencies higher than 10 MHz, the electrophysiological properties of the eukaryotic

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Article highlights.

- Tumor treating fields (TTFields) are low intensity (1 – 2 V/cm), intermediate frequency (100 – 200 kHz) alternating electric fields, which can induce apoptosis.
- TTFields are able to inhibit tumor growth in various cell lines and animal models.
- The combination of TTFields with several cytotoxic agents resulted in a supra-additive tumor growth inhibition *in vitro* and *in vivo*.
- Two clinical trials, a Phase III trial in glioblastoma multiforme (GBM) and a Phase II study in non-small cell lung cancer (NSCLC) have shown antitumor activity of TTFields.
- Toxicity was low; it consisted mainly of skin reactions at the site of the electrodes.

This box summarizes key points contained in the article.

membrane lead to dielectric polarization that eventually heats the tissue [4,5]. Intermediate-frequency alternating electric fields, at frequencies between 10 kHz and 1 MHz, neither cause net depolarization nor significant dielectric losses, therefore, cannot stimulate nerves/muscles, but also cannot seriously heat tissues at low enough intensities. It was thought that such electric fields have no meaningful biological effect on cells [4,6-9]. Nevertheless, it was recently found that such fields, named tumor treating fields (TTFields), have an antimitotic activity and may lead to the death of dividing cells. The fields were found to have these properties already at a very low intensity (< 2 V/cm) and at intermediate frequency of 100 – 300 kHz.

2. TTFields's mechanism of action

Each cell contains numerous electrically charged molecules, such as proteins and DNA. Under an alternating electric field, these molecules will oscillate according to the changing direction of the field and its density (Figure 1). If the field is uniform, the forces acting intermittently to opposite directions will cause a movement parallel to the direction of the field. When the frequency of the field is high enough, such as in the case of TTFields, this molecular movement will reduce. In the case of dipoles, where there is an electric split between the positive and negative poles of a molecule, it will align with the direction of the electric field and remain at the same place. All charged molecules, including dipoles, will move toward the higher field density in a non-uniform alternating electric field. Within a non-dividing cell, the field is mostly uniform and the net force on charges and dipoles will, therefore, yield minimal movement. Non-uniform electric fields, on the other hand, force polar molecules to move toward higher field intensity, in a process called dielectrophoresis [10,11]. Such fields are characteristic of dividing cell when a narrow furrow connects the two forming daughter cells.

2.1 Arrest of mitotic spindle formation

Mitotic spindle is the organelle that separates the cell's chromosomes to each of the daughter cells during mitosis. The arms that hold to the chromosomes consist of small polar molecules called tubulins, which polymerize to form a 'chain' of subunits that will reach the genetic material at the center of the cell. As noted before, the field is uniform within the non-dividing cells, but the tubulin subunits will tend to align according to the direction of the field. Finite element simulations showed that the electrical forces acting on the subunits prevent them from attaining the orientation required for efficient polymerization, therefore, mitosis becomes arrested for an abnormally long time [12]. This happens since subunits far enough from the growing microtubule will be subjected to an electric force strong enough to prevent further polymerization. When this process takes place, cells could either complete mitosis or disintegrate.

2.2 Mitotic furrow destruction

Not all cells seem to be affected by means of disruption of mitotic spindle formation. The membranes of cells that completed metaphase will start dividing into two daughter cells, pulling the daughter chromosomes to each of the cells' poles. During the last step in mitosis, that is, cytokinesis, a cleavage furrow is eventually formed, which completes the process of cell separation. This narrow membranous link results in an hourglass-shaped non-uniform electric field, unlike non-dividing cells, in which the electric field is uniform. During cytokinesis, the densest electric field is found in the narrow center. This focusing of the field directs all electric charges and dipoles to the furrow due to the unidirectional character of the electric force (dielectrophoretic force) under this condition. Finite element simulations have shown that polarized molecules and organelles within the cell will be affected by forces high enough to move toward the furrow so as to disrupt the internal cell structure and cause the cell destruction seen under TTFields therapy [12].

3. Preclinical studies with TTFields

A number of preclinical trials have shown the efficacy of TTFields in the inhibition of cancer cell proliferation and their destruction *in vitro* [12,13]. Many cell lines were cultured and tested under TTFields, among others melanoma, glioma, lung, prostate and breast cancers. TTFields was applied continuously for 24 – 72 h. In all cases, proliferation was significantly inhibited, compared with control cultures and to non-replicating cultures (baby hamster kidney (BHK) cells) treated with TTFields. For some of the cell lines, a specific optimal frequency that demonstrated maximal inhibitory effect was found, possibly reflecting different cell size and shape (Table 2) [13]. Under time-lapse microscopy, cancer cells demonstrated significantly prolonged mitosis and even cell destruction on the formation of the cleavage furrow. Immunohistochemistry studies of cell cultures treated with TTFields showed many abnormal

Table 1. Alternating electric fields used in medicine

Frequency	Biological activity	Application
< 1 kHz	Membrane depolarization	Defibrillators, ECT, bone growth, fracture healing, ICD
100 – 300 kHz	Mitotic arrest and apoptosis	TTFields
1 – > 10 MHz	Dielectric polarization	Diathermy, radio frequency tumor ablation

ECT: electroconvulsive therapy; ICD: implantable cardioverter-defibrillator; TTFields: tumor treating fields.

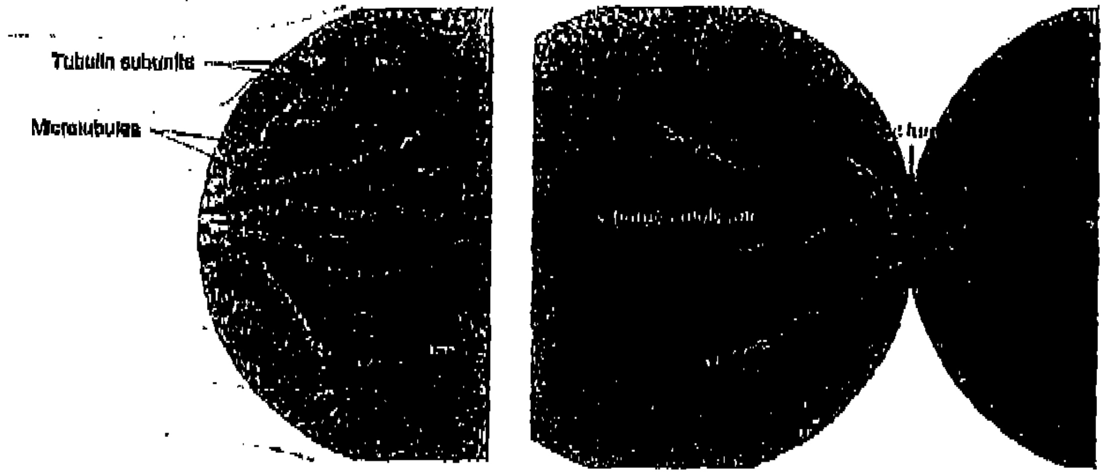

Figure 1. Antimitotic effects of tumor treating fields (TTFields). At the beginning of mitosis, the electric field is uniform within the cell, causing tubulin subunits to align with the direction of the field and inhibiting their polymerization to form a normal microtubule spindle. In a non-uniform electric field formed during cytokinesis, charges and dipoles move toward the high field density at the mitotic furrow, disrupting mitosis and disintegrating the daughter cells.

mitotic figures that could be related to the interference of TTFields with the mitotic spindle formation. These figures resemble the presentation of cancer cells treated with agents that interfere with mitotic spindle formation, such as paclitaxel. Further experiments showed that the efficacy of TTFields in combination with different chemotherapies is additive and could be synergistic [14].

Interestingly, TTFields caused cultured cells to orient in the direction of the electric field [12]. This could be explained by the fact that the electric forces are maximal when the axis of division is aligned with the external field. This also implies that the angle of the cell affects its vulnerability to TTFields during mitosis.

TTFields was also shown to inhibit tumor growth in several mouse, rat and rabbit animal models [12,13]. Implanted cell lines were used to test the most effective frequency and intensity for this *in vivo* treatment. Postmortem analysis of the treated animals showed a significant tumor size reduction in the case of TTFields-treated animals, compared with control animals. No difference of the local temperature in the vicinity of the tumor was found between the two groups. *In vivo* experiments showed that it is possible to deliver the field to the target region using insulated non-invasive electrodes. While there was no statistically significant inhibition of tumor growth when a unidirectional TTFields was delivered this way, two- and three-directional fields led to a statistically significant growth inhibition [13]. *In vivo* tumor models have shown the same optimization in tumor inhibition when using the effective specific frequency for each cell type. No abnormality in vital signs, electrocardiograms (ECG), complete blood counts (CBC), chemistry and coagulation panels was found during the follow-up period of animals treated with TTFields, and no treatment-related pathologies were found postmortem.

In a metastatic melanoma mouse model and metastatic kidney cancer rabbit model, TTFields was shown to reduce the extent of metastatic spread, possibly due to metastasis growth inhibition, migration capability impairment and primary tumor local control [15].

4. Clinical studies with TTFields

Prior to applying TTFields to human patients, feasibility was tested using finite element mesh (FEM) simulations and measurements within the brain of a volunteer undergoing brain

Table 2. Optimal TTFields frequency for tested cell lines

Cell line	Optimal frequency (kHz)
B16F1 (mouse melanoma)	120
AA8 (Chinese hamster ovary)	150
VX-2 (rabbit kidney)	150
MCF-7 (human breast)	150
MDA-MB-231 (human breast)	150
F-98 (rat glioma)	200
U-87 (Human glioma)	200
U-118 (Human glioma)	200

TTFields, tumor treating fields.

surgery. It was found that TTFields can be effectively applied to the cerebrum using surface electrodes. TTFields was first tested on 10 recurrent malignant glioblastoma multiforme (GBM) patients. No concomitant chemotherapy was used during the clinical trial, and TTFields was the only antitumor therapy. TTFields was delivered via a portable, light-weight (~ 3 kg) device carried by the patient (NovoTTFields-100A, NovoCure Ltd, Haifa, Israel), connected to two pairs of insulated electrodes that were applied to the patients' skin. The device continuously (18 h/day on average) delivered two perpendicular 1 – 2 V/cm, 200 kHz alternating electric fields (Figure 2). Patients had a highly significant increase in the median time to disease progression (26.1 weeks) and progression-free survival (PFS) at 6 months (50%) compared with historical controls, with a median overall survival (OS) of more than 62 weeks [13]. In addition, no treatment-related serious adverse event was detected in a total of 280 treatment weeks. The only treatment-related adverse event was mild-to-moderate contact dermatitis beneath the electrode gel, which was easily managed using topical treatments.

These preliminary findings led to a Phase III clinical trial of TTFields compared with best standard of care chemotherapy in 237 patients with recurrent GBM [16,17]. Patients in this study were previously treated with an unlimited number of surgeries/chemotherapy cycles. They were randomized to either a TTFields arm, given as a monotherapy without additional antitumor treatments, or to the best standard chemotherapy (BSCh) arm, which was at the treating physician's discretion. TTFields was administered continuously and patients' compliance was excellent, with a median duration of 20 h/day. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky performance status (KPS) of 80%. Mean treatment duration was 4.4 months in the TTFields group versus 2.3 months in the BSCh group. In the group of 185 patients who were treated per protocol, a statistically significant survival benefit was seen for the TTFields group (median OS 7.8 vs 6.1 months for TTFields and BSCh, respectively). Moreover, patients with better prognostic baseline characteristics (KPS 80% or higher, age 60 or lower) demonstrated an even higher survival benefit when treated with TTFields (median OS 8.8 vs 6.6 months; n = 110). These results show that TTFields as a monotherapy are at least as effective as the best available chemotherapy or supportive care in this poor prognosis disease. It is noteworthy that quality of life (QOL) was equivalent or superior in patients treated with TTFields compared with BSCh. This clinical trial also showed that the only TTFields-related adverse events were mild-to-moderate contact dermatitis beneath the electrodes in a minority of patients. The incidence of toxicities was significantly higher in the BSCh arm.

TTFields was also explored in a Phase I/II single arm study in combination with pemetrexed for advanced (stage IIIB/IV) non-small cell lung cancer (NSCLC) as a second-line treatment, after failure of standard first-line chemotherapy [18]. Electrodes were applied to the chest and upper abdomen and the device (NovoTTFields-100 L, NovoCure Ltd) generated 150 kHz TTFields, in accordance with the preclinical findings relating to lung cancer cell lines. Forty-one patients were treated, including 7 (17.1%) with squamous cell carcinoma and 30 (73%) with stage IV disease. The device was well tolerated and the average daily use was 11.2 h. No TTFields-related serious adverse event was reported for a cumulative time of over 720 weeks. Median PFS was 22 weeks and in-field PFS (i.e., PFS within the area of the TTFields; the study's primary end point) in the lungs and liver was 28 weeks. This is an important finding because it can be assumed that in the same patient the higher tumor control within the TTFields area was a specific effect of TTFields. Median OS was 13.8 months and 1-year survival was 57% (Figure 3). Six patients (14.6%) had a radiological partial remission (PR) and 16 patients had stable disease (SD) (39%). These results are very promising and compare extremely well with matched historical controls treated with pemetrexed alone in second-line treatment [19].

Special attention was given to potential adverse events using TTFields: in the glioblastoma trial careful neurological examination and documentation was required once a month. In the lung cancer trial, ECGs were mandated at the beginning of the trial, during the treatment if adverse effects occurred and at the end. Finally, skin reactions were monitored at every visit and documented according to the National Cancer Institute (NCI)-Common Toxicity Criteria (CTC) (version 3.0) in all studies. All other adverse events were monitored routinely at every visit according to the CTC criteria. In all studies involving TTFields the only side effect, which occurred more frequently was grade 1 – 2 skin toxicity. In the glioblastoma trial there was a direct control group, in the lung cancer trial we compared the side effects with the large Phase III study by Hanna *et al.*, in which pemetrexed was given as a second-line treatment [19].

5. Summary

TTFields was shown to inhibit proliferation and to cause cell destruction of many cancer cells *in vitro* and *in vivo*. In addition, TTFields significantly improved human patients' prognosis in recurrent GBM and probably also in NSCLC. At the time this review was submitted, there were no serious adverse events found related to TTFields.

Figure 2. The tumor treating fields (TTFields) generating portable device (NovoTTFields-100A).

On the contrary, the treatment was toxicity-free for treated patients, except for mild-to-moderate contact dermatitis underneath the electrodes. Importantly, there were no cardiac or neurological abnormalities as a result of TTFields treatment. The use of non-invasive surface electrodes prevented flow of ionic currents [20,21] or cell death [22] as a result of direct currents, and thus decreased skin damage and enabled continuous treatment.

TTFields can actively inhibit different cell types, including multi-drug-resistant (MDR) ovarian and breast cancer cell lines that overexpress ABC (ATP-binding cassette) transporters [23]. It may not only be useful in the treatment of locally advanced tumors, but also in the prevention and treatment of metastatic disease. TTFields has the potential to inhibit the migration of metastases from a primary tumor, it can inhibit the growth of metastases in the lungs once they have been seeded in the target organ, through the presence of the fields in the lungs themselves.

In the first Phase III study published to date [16,17], TTFields had minimal toxicity and patients' compliance was excellent, over an extended period of time. The application of TTFields resulted in an improved median OS, higher response rate and longer time to treatment failure compared with best standard chemotherapies and also led to an improvement in many QOL parameters. A large-scale Phase III clinical trial in newly diagnosed GBM is currently being conducted.

In the first clinical trial for NSCLC patients, TTFields was well tolerated in a second-line setting. It was safe and efficacy end points were excellent, compared with historical data for pemetrexed alone [19].

The good safety profile along with the significant clinical efficacy and QOL advantages make TTFields an attractive treatment in GBM, and perhaps in many other malignancies.

6. Expert opinion

TTFields is a novel and promising concept for treating solid tumors. *In vitro* and *in vivo* experiments have repeatedly shown a significant inhibitory effect on cancer cell proliferation upon application of TTFields. We already know that at least two physical mechanisms are involved: the first is interference with the mitotic spindle formation as a result of electric forces preventing the normal polymerization of the tubulin subunits. The second mechanism results from the non-uniformity of the electric field in the context of cytokinesis, and the movement of molecules in the direction of the mitotic furrow as a result of the unidirectional force generated by TTFields.

There are also some data indicating that combining chemotherapeutic cancer treatments with TTFields may increase efficacy and sensitivity to chemotherapy [14]. Several tumor types are sensitized to radiation after adding different chemotherapies, even at low doses [24-26]. Could some tumors similarly be more susceptible to TTFields treatment if treated concomitantly with certain cytotoxic agents? This is a plausible idea, since TTFields acts on specific organelles (e.g., the mitotic spindle), which are also the target of some of the anticancer drugs. Taxanes act through stabilizing the link between tubulin dimers in the spindle microtubules. It could be that the abnormal increase in microtubule length caused by this class of agents, which leads to the formation of a larger dipole moment, results in an increase in the efficacy of TTFields [14]. This possible synergism could be used to achieve a better response, but alternatively also as a way to decrease chemotherapy intensity in patients who cannot tolerate the toxicity of full-dose chemotherapy. The fact that TTFields itself was not toxic and in combination with pemetrexed did not increase the known side effects of the latter in the clinical trials mentioned above, makes combination therapies an attractive therapeutic option.

Preclinical experiments showed the frequency-dependant effect of TTFields, with different frequencies showing a maximal inhibitory effect in certain cancer cell types [15]. In the future, it will be interesting to see how this characteristic could be exploited in order to maximize the effect, by adjusting the frequency on an individual tumor basis, using cytological/pathological specimens for the analysis. Such adjustments could be possible for tumors of the same entity but in different patients, and maybe even at different stages in the course of the same disease.

Other fields of interest that will probably be investigated in the future include the pathway in which cell death occurs following exposure to TTFields. Unpublished findings show that apoptosis is the process that leads to cancer cell death

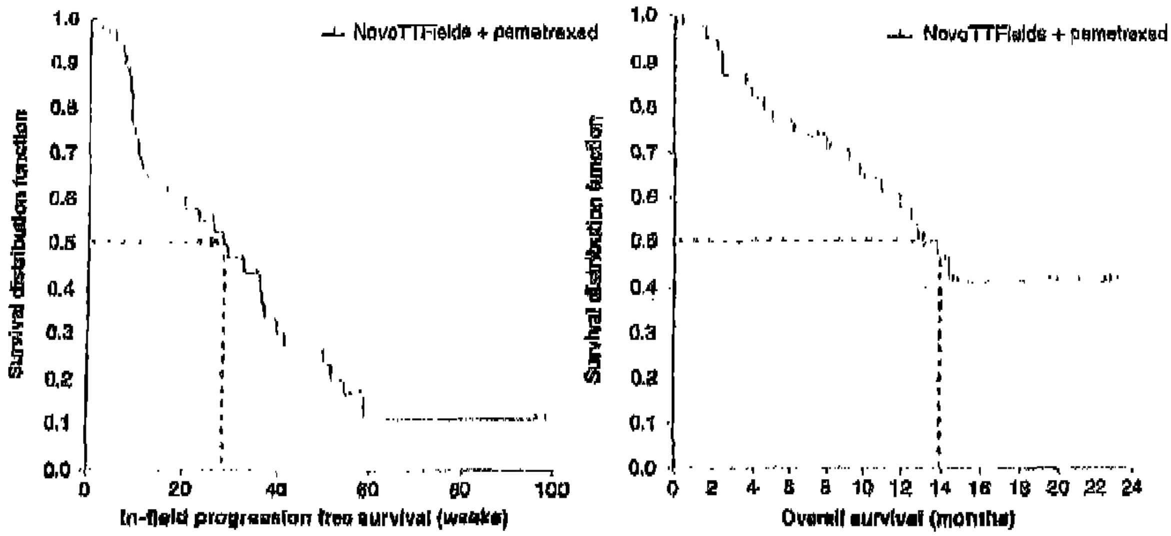

Figure 3. Phase II trial using tumor treating fields (TTFields) in combination with pemetrexed in non-small cell lung cancer as a second-line therapy. Median in-field progression-free survival (PFS) was 28 weeks. Median overall survival (OS) was 13.8 months; n = 41.
Adapted from poster presentation ESMO 2010 [18].

under TTFields. Finding the specific pathway through which apoptosis is carried out will provide a better understanding of the basic mechanism and will pave the way for other combinations or treatment optimization. The immune system plays an important role in the pathogenesis of cancer [27]. TTFields has the potential to beneficially affect the microenvironment of the tumor: it could act directly on recruited immune cells, alternatively, it could change the interaction between these cells and the tumor following changes to the tumor cell structure, vasculature, etc. Preliminary data show that there is a change in the presence of immune cells that interplay with cancer cells, following TTFields treatment [15].

Both the Phase III (for recurrent GBM patients) and the Phase II (for advanced NSCLC) trials have given some important insights on using TTFields [16-18]. The high compliance demonstrates that it is feasible to administer TTFields continuously using a light-weight portable device, in spite of the necessity to be attached to the device. Since most patients enrolled in the trials were somewhat hindered by their malignant disease, they generally adjusted to TTFields quite quickly and well. In the NSCLC trial, the majority of patients used TTFields overnight and was free at daytime. It can be assumed that other cancer patients will tolerate TTFields as well. It will be interesting to see how other chemotherapies administered concomitantly to TTFields will affect the course of these patients. A Phase III trial (NCT00916409) for newly diagnosed GBM patients treated with a combination of temozolomide and TTFields is currently ongoing.

As a physical treatment modality, TTFields has the potential to be active in other solid tumors as well. In a pilot study, TTFields therapy was very well tolerated and safe for four patients bearing skin lesions from breast and melanoma tumors. These tumors showed transient inhibition in the growth rate during a 2- to 4-week treatment and the findings warrant further investigations [28]. While systemic chemotherapy usually has significant toxicities, biologically targeted therapies often affect only a subset of tumors carrying specific mutations or proteins. Glioblastoma and NSCLC, like many other tumors, harbor many different genotypes [29-31] and it has been difficult to show a major impact of chemotherapy or even targeted agents in these tumor types, at least for the majority of patients. TTFields acts independently of the expression of cell surface receptors or other tumor biomarkers. There are no alternative mitosis mechanisms, thus cancer cells are unlikely to be or to become resistant to TTFields.

There are several ways of further developing TTFields clinically. TTFields is a regional treatment: it could be employed in situations where radiotherapy is not possible anymore, for example, after a full course of radiation to the brain. Another option would be to test it in situations in which prophylactic radiotherapy is used: for example, prophylactic cranial irradiation (PCI) small cell lung cancer, hopefully circumventing the late toxicity of PCI. Lastly, it can of course be tested together with radiotherapy. Even though TTFields is a regional treatment, it still managed to decrease the likelihood of metastases formation in animal experiments [15], the most common cause of death in cancer. It could be that TTFields was able to prevent malignant cell evasion from the primary tumor in the lung cancer treated population, thereby leading to decreased formation of micrometastases [18].

In summary, TTFields could be considered as a potential effective treatment for patients suffering from different cancer types. The non-toxic characteristics and promising clinical outcomes in several clinical trials conducted to date should encourage investigators to further evaluate TTFields, either as a monotherapy or in combination with other treatments.

Declaration of interest

M Pless declares no conflicts of interest. U Weinberg works for NovoCure Ltd. as Medical Director. Novocure has supported experiments described in this review and was the sponsor for the clinical trials. The paper was not supported by a commercial company.

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[redacted]

JULY 2, 2013

[redacted]

RE: [redacted]
Medicare Number: [redacted]

Dear [redacted]

This letter is about our decision in your appeal to ANTHEM BLUE CROSS LIFE AND HEALTH INS COMPANY (Anthem). You asked Anthem to pre-approve the NovoTTF 100-A system (electrical field therapy) for [redacted]

Our decision

We agree with you. This means that we will tell Anthem to pre-approve the NovoTTF 100-A system. To learn more about how we made our decision, read the following pages of this letter.

What you have to do

We sent Anthem a copy of this letter, so they know they have to pre-approve the NovoTTF 100-A system.

Make sure the Novo TTF 100-A system is obtained through Anthem. Otherwise, Anthem may not pay for it.

Anthem has to pre-approve the item or service or make plans to pre-approve the item or service within 72 hours. If Anthem does not do so within 72 hours, call the Chicago CMS Regional Office at 312-353-7180

[redacted]

Chicago CMS Regional Office

Medicare
Managed Care & PACE
Reconsideration Project

Reviewing Medicare Appeals

MAXIMUS Federal Services
Medicare Part C QIC
3750 Monroe Ave, Suite 702
Pittsford, New York 14534
Tel: 585-348-3300
Fax: 585-425-5292
www.medicareappeal.com

Who We Are

We are MAXIMUS Federal Services. We are experts on appeals. Medicare hired us to review the file and decide if the health plan made the correct decision. We work for Medicare. We do not work for the health plan.

Katy Hanson
Project Director
Medicare Managed Care & PACE Reconsideration Project

Do you need help?

Call 1-800-MEDICARE (1-800-633-4227) for help or more information about what you can do in this case. TTY users should call 1-877-486-2048.

PAGE 2/4 [redacted]

How we made our decision

1. We read all the papers in the file.
2. We checked Medicare rules.
3. We checked the contract with Anthem.
4. We sent the file to a MAXIMUS Federal Services Doctor Consultant.

To make our decision we read all the papers in the file very carefully. We used the Medicare rules. We looked to see if Anthem correctly followed Medicare rules and regulations.

Medicare rules say that the health plan must give the member a subscriber agreement. It is a contract between the health plan and the member. It is usually called the "Evidence of Coverage" (EOC) or "Member Agreement." We read this contract carefully to see what Anthem is supposed to cover.

We sent the case to a MAXIMUS Federal Services Doctor Consultant. This doctor works for us, not the health plan. We asked this doctor to review all of the medical records in the file.

Medicare rules

The rules say that health plans must pay for a medical service or item if regular Medicare would pay for it in this case. You can find this rule at 42 CFR §422.101.

The rules say that medically necessary services are those that are reasonable and necessary for the diagnosis or treatment of an illness or injury. Medically necessary services include services to improve the functioning of a malformed body member. You can find this rule at Social Security Act § 1862 (a)(1)(A).

If you want to read these Medicare rules, you can go to this web site www.medicareappeal.com.

The health plan contract

The health plan contract says that Anthem covers items and services in accordance with Medicare rules

Doctor review

Our MAXIMUS Federal Services Doctor Consultant looked at the file for this case. This doctor says that the NovoTTF 100-A system is medically necessary for [redacted] Our doctor found that the patient presented in October 2012 with headaches, confusion and left hemiparesis. A MRI scan revealed a right fronto-temporal mass that was resected by December 2012. The pathology showed this tumor was a glioblastoma multiforme, WHO grade IV. She got temozolomide and concurrent radiation therapy but the tumor progressed. She had more surgery in March 2013 after which the NovoTTF device was recommended. In 2011, the FDA approved the NovoTTF-100A device to deliver alternating electrical fields to treat recurrent GBM. The device has FDA approval and is appropriate to use in this patient who has exhausted standard chemotherapy options.

Explanation of decision

We decided that Anthem has to pre-approve the NovoTTF 100-A system (electrical field therapy) [redacted]

You asked Anthem to pre-approve the NovoTTF 100-A system. You say that this device is the only promising option for the patient at this time. Due to her orphan disease status, limited treatment options and favorable outcome and higher quality of life afforded with this treatment, you are requesting reconsideration of the denial. Anthem denied your request. Anthem says that the level of evidence is 2B (equivocal) in the current NCCN guidelines which is not sufficient to warrant medical necessity.

Anthem must follow Medicare rules. Medicare rules say that if there are no specific coverage rules for an item or service, then that item or service will be covered when it is medically necessary.

Our MAXIMUS Doctor Consultant says that the NovoTTF 100-A system is medically necessary for [redacted] We looked at this doctor's review, the file and Medicare rules. Based on this information, we decided that Medicare rules for coverage of the NovoTTF 100-A system have been met. Therefore, we decided that Anthem has to pre-approve the NovoTTF 100-A system (electrical field therapy) for [redacted]

If Anthem does not agree with our decision, they can ask us to open a case again. We only open a case again if we believe there was a mistake or if there is new information to review. The health plan has to show us the mistake and/or send us the new information. This does not happen often. If we decide to open the case again, we will send you a letter.

H

Referral to/from Contractor Medical staff

I

Contractor Medical Policies

J

LIST OF RELEVANT PORTIONS OF THE LAW, REGULATIONS, CMS RULINGS

____ L11449 Surgical Dressings
http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11449&ContrId=140&ver=58&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AgACAAIAAAAAAA%3d%3d&

____ L11525 Therapeutic Shoes for Persons with Diabetes
http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11525&ContrId=140&ver=36&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AgACAAIAAAAAAA%3d%3d&

____ L11526 Tracheostomy Care Supplies
http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11526&ContrId=140&ver=30&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AgACAAIAAAAAAA%3d%3d&

____ L28616 Transcutaneous Electrical Joint Stimulation Devices (TEJSD)
http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=28616&ContrId=140&ver=3&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AgACAAIAAAAAAA%3d%3d&

____ L5031 Transcutaneous Electrical Nerve Stimulators (TENS)
http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=5031&ContrId=140&ver=46&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AgACAAIAAAAAAA%3d%3d&

____ L34665 Tumor Treatment Field Therapy (TTFT)
http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34665&ContrId=140&ver=3&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AgACAAIAAAAAAA%3d%3d&

____ L11566 Urological Supplies
http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11566&ContrId=140&ver=52&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AgACAAIAAAAAAA%3d%3d&

____ L34675 Vacuum Erection Devices (VED)
http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34675&ContrId=140&ver=5&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AgACAAIAAAAAAA%3d%3d&

K

Overpayment Extrapolation Materials

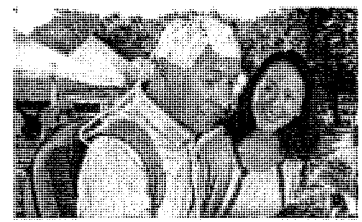
L

MRN/Other

MedTech

Brain tumor treatment device gets early trial halt for efficacy as a combo with chemo

by Stacy Lawrence | Nov 18, 2014 7:10am



Optune in action--Courtesy of Novocure

The only FDA-approved, wearable cancer treatment device may expand its reach. A Phase III trial of Optune (NovoTTF-100A System) from Novocure was halted early due to statistically significant efficacy for the device in combination with chemotherapy to treat newly diagnosed glioblastoma patients.

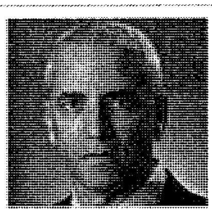
This is an expansion upon its original indication approved by the FDA in 2011 for use as a monotherapy for recurrent glioblastoma after surgical and radiation options have been exhausted.

Founded in 2000, the startup has spent about $250 million in pursuit of a tumor treatment device. Despite this massive infusion of cash--or perhaps because of it--Novocure remains a private company. It has at least three big, strategic corporate investors: Medtronic ($MDT), Pfizer Venture Investments and Johnson & Johnson Development Corporation. In addition, WFD Ventures and Index Ventures back the somewhat controversial company. Device companies have a checkered history when it comes to efficacy in cancer treatment.

The idea is to create tumor-treating electric fields that are delivered locally to the body via transducer arrays that are worn directly on the scalp. Patients must commit to wearing the obtrusive device at least 18 hours daily. The electric fields are designed to disrupt the process of cell division in the tumor, which divide at an accelerated rate compared with normal tissue. The company says the frequency is tuned to target only tumor cells, which are a certain size.

The new data from the EF-14 trial show that newly diagnosed glioblastoma patients treated with the device in combination with chemotherapeutic agent temozolomide have a statistically significant improvement in progression-free survival and in overall survival as compared with temozolomide alone. Specifically, the device and the chemo provided a median PFS of 7.1 months versus 4 months for temozolomide alone, while the combination offered 19.6 months median OS versus 16.6 months for temozolomide only.

After the first two years of the study, 43% of the patients in the device/temozolomide arm remained alive, while only 29% of the patients in the temozolomide were living. The trial was halted for efficacy, in order to offer the treatment to the remaining chemo-only group. The Independent Data Monitoring Committee conducted this prespecified interim analysis on the first 315 patients, which represented about half of the targeted trial population



Novocure CEO Asaf Danziger

"These results are spectacular," Dr. Roger Stupp, director of the University Hospital Cancer Center at the University of Zurich and EF-14 principal investigator, said in a statement. "A new standard of care for patients suffering from glioblastoma is born."

Glioblastoma is the most common form of primary cancer in the brain, with about 10,000 patients diagnosed annually in the U.S. In addition to glioblastoma, Novocure is also in pilot testing for treatment of ovarian, pancreatic and non-small cell lung cancer as well as brain metastases. Its system was recently renamed Optune.

Novocure CEO Asaf Danziger added that the startup is "working closely with FDA" to make the device available to newly diagnosed glioblastoma patients "as soon as possible."

- here is the release on the data
- and here is a *New York Times* **story** that offers a poignant patient perspective (sub. req.)

Bad Blood: The book that reads like a late-night biotech horror movie | FierceBiotech

DEPARTMENT OF HEALTH & HUMAN SERVICES
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CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES
CENTER FOR MEDICARE

Center for Medicare

Michael Abrogi
Novocure, Inc.
195 Commerce Way
Portsmouth, NH 03801

NOV 27 2013

Re: 13.069

Request to establish two new Level II HCPCS codes: one code (Request #13.069A) - to identify a Tumor Treating Fields (TTFields) Electronic Field Generator and System Components, trade name: NovoTTF-100A; and one code (Request #13.069B) to identify the Insulated Transducer Array for use with the TTFields device.

Dear Mr. Abrogi:

On behalf of the Centers for Medicare and Medicaid Services (CMS), I would like to thank you for your application to modify the HCPCS Level II code set. The HCPCS Level II code set is available for use by all payers, and is maintained by CMS taking into consideration the national program operating needs of all payers, including Medicare, Medicaid, and Private Insurers.

CMS reviewed your application and published the following preliminary decision:

A national program operating need was not identified by Medicare, Medicaid, or the private insurance sector to establish a code to identify the devices that are the subject of this request.

We appreciate the comments that were provided at CMS' HCPCS Public Meeting in reaction to our preliminary decision. Specifically, the designated primary speaker disagreed with CMS' preliminary recommendation stating that a national program operating need exists to establish the 2 new codes requested on the bases that: 1) the subject treatment is widely used at home for treatment of Glioblastoma; 2) private insurers are "covering" the device "as DME" using code E1399; 3) the subject system is functionally distinct from any other form of electrical therapy; and 4) the processing time for use of unlisted codes cuts into patient's remaining life.

The CMS HCPCS Workgroup reconvened to consider all input received, and revised its decision. The following modification has been made to the HCPCS Level II standard, national code set:

Establish E0766, Electrical Stimulation Device Used For Cancer Treatment, Includes All Accessories, Any Type

Establish A4555, Electrode/tranducer for use with electrical stimulation device used for cancer treatment, replacement only

All changes to the code set are effective January 1, 2014, unless an earlier effective date is specified in the 2014 Annual HCPCS Update. The entire 2014 HCPCS Annual Update will be available and can be downloaded free of charge at: http://www.cms.hhs.gov/medhcpcsgeninfo. The code set is searchable using the edit function and key words or code numbers.

Questions regarding classification of products into HCPCS Level II code categories should be submitted to the insurer in whose jurisdiction a claim would be filed. For private sector health insurance systems, please contact the individual private insurance entity. For Medicaid systems, please contact the Medicaid Agency in the state in which the claim is being filed. For Medicare, contact the Medicare contractor.

Sincerely ,

Cynthia Hake

Cynthia Hake,
Deputy Director, CM, Division of DMEPOS Policy
Director, CMS' National HCPCS Coding Program

TTFields Peer Reviewed Publications

Alexiades N, McKhann GM. A Shock to the System: Tumor-Treating Fields Plus Temozolomide for Glioblastoma. *Neurosurgery*. 2018 May 1;82(5):E115-E116. doi: 10.1093/neuros/nyy044.

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DECLARATION OF JUSTIN KELLY, RN, BSN
July, 2018

1. I, Justin Kelly, make the following statement regarding my own personal knowledge and experience, and if called upon, could competently testify to the issues herein.

2. I received my BSN, magna cum laude, from the University of Massachusetts, Boston.

3. I have worked for Novocure since November 2011 and I currently am the Regional Vice President, Health Policy.

4. A large body of peer-reviewed literature shows that tumor treating fields, also known as alternating electric fields, disrupt the cell division process in cancerous tumors which may lead to programmed cell death or apoptosis. Tumor treating fields have shown statistically significant improvement in patient survival and outcomes in glioblastoma multiforme brain tumors compared with traditional standard of care alone.

5. Novocure's Optune device was FDA-approved through the Premarket Approval ("PMA") pathway for the treatment of adult patients with recurrent glioblastoma in April 2011. In 2015, the FDA-approved the Optune device for the treatment of adults with newly diagnosed glioblastoma in combination with temozolomide chemotherapy after completing radiation therapy.

6. Since the Optune device was FDA-approved, more than 800 leading oncology centers throughout the United States have been certified to provide and prescribe Optune.

7. Optune has been prescribed by more than 1200 providers in at all 50 states, Puerto Rico and the District of Columbia. As of July 18, 2018, the Optune device has been prescribed for over 7200 patients in the United States.

8. The Optune device and its clinical effectiveness have been described in over140 peer-reviewed publications. See Attachment hereto for an abbreviated bibliography highlighting results from our pivotal trials.

9. The Optune device has been accepted by the relevant clinical community as a treatment to improve the clinical outcomes and extend the survival of patients diagnosed with a glioblastoma.

10. More than 35 commercial payers, including virtually all the large national payers, deem Optune to be reasonable and medically necessary for beneficiaries diagnosed with a glioblastoma, and provide coverage for the device through published coverage policy. Furthermore, several Medicaid states have adopted positive coverage policies for Optune.

11. I certify, under penalty of perjury that the foregoing is true and correct to the best of my knowledge. Executed this 23rd day of July 2018.

Justin Kelly, RN, BSN

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List of Exhibits

Ex. 1 FDA SSED Recurrent Dz - Mar 2011

Ex. 2 NovoCure FDA Panel Minutes - March 2011

Ex. 3 1-CBTRUS Statistical Report - 2012 . ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 4 2-NCCN Guidelines_2013 . CMS Exhibit 4 . Unable to Add Bates Numbering ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 5 3-Rosenfeld_TxRecurrent Gliomas_CommOnc 2011 . ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 6 4-Salzberg_Abstract -TTF Pilot_Onkologie 2008 . ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 7 5-Novocure Overview Website . ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 8 6-FDA SSED_Mar 2011 . ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 9 7-Kirson_TTF_PNAS 2007 . ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 10 8-Stupp_Phase III TTF_EurJCancer 2012 . ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 11 9-Stupp_Abstract TTFvsBSC_JClinOnc 2010 . ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 12 10-AlbertaHealthSer - GBM_Sept 2012 . ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 13 11-Horizon Scan TTF_Jun 2009 . ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 14 12-AU Tech Brief TTF_2012 . ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 15 13-Pless - TTF Review-ExpOpin 2011 . ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 16 14-AETNA Coverage Policy - Updated 3-19-13 and 12-27-13 . ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 17 15 - Anthem Coverage Policy - TTF- Updated 11-8-12 and 11-14-13 . ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 18 16-Baehring_GBM CurTx and FutPer_HemOnc ClinNA 2012 . ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 19 17-Yin et al._GBM Tx Review_CritRevOncHem 2013 . ; **Description**: SOURCE OF INFORMATION INCLUDED IN BIBLIOGRAPHY

Ex. 20 Hau et al -Salvage Tx GBM_Cancer 2003 . ; **Description**: Additional Articles/Informational Sources

Ex. 21 Medscape_GBM_Sept 2013 . ; **Description**: Additional Articles/Informational Sources

Ex. 22 Neuro Manifestations BGM_2012 . ; **Description**: Additional Articles/Informational Sources

Ex. 23 Pless Abstract Review TTF_ExpOpinInvDrg_2011 . ; **Description**: Additional Articles/Informational Sources

Ex. 24 Rulseh et al. WJSO 2012 . ; **Description**: Additional Articles/Informational Sources

Ex. 25 Salzburg_NovoTTF solid tumors - Onkologie 2008 . ; **Description**: Additional Articles/Informational Sources

Ex. 26 Schroeder_Editorial on Salzberg_Onkologie 2008 . ; **Description**: Additional Articles/Informational Sources

Ex. 27 Wong_CaMed 2014 . ; **Description**: Additional Articles/Informational Sources

Ex. 28 Wong_Novo vs MD Choice_Cancer Jan 2014 . ; **Description**: Additional Articles/Informational Sources

Ex. 29 NCCN guidelines-Palliative Care_2013 . Protected Version . Ex. 29; **Description**: Additional Articles/Informational Sources

Ex. 30 Villano-Delayed_response_and_survival_from_NovoTTF-100A_in_recurrent_GBM-1. Protected Version . Ex. 30 ; **Description**: Additional Articles/Informational Sources

Ex. 31 Response to Comments - TTFT - Final . June 2014 .

Ex. 32 TTFT LCD and PA - Draft for Distribution .

Ex. 33 LCD and PA TTFT - MCD Archive

Ex. 34 ESMO - Glioblastoma Guidelines - Ann Onc 2014 .

Ex. 35 BCBST - Coverage Policy - TTF - 2-9-14 .

Ex. 36 NCCN Guidelines - CNS cancers - Cat 3 - 2014 . CMS Exhibit 36

Ex. 37 TTFT Timeline .

Ex. 38 Open Meeting announcement 121713 2of2 . CMS Exhibit 38

Ex. 39 DRAFT_CNS-009-guideline_2013-01-26 . CMS Exhibit 39

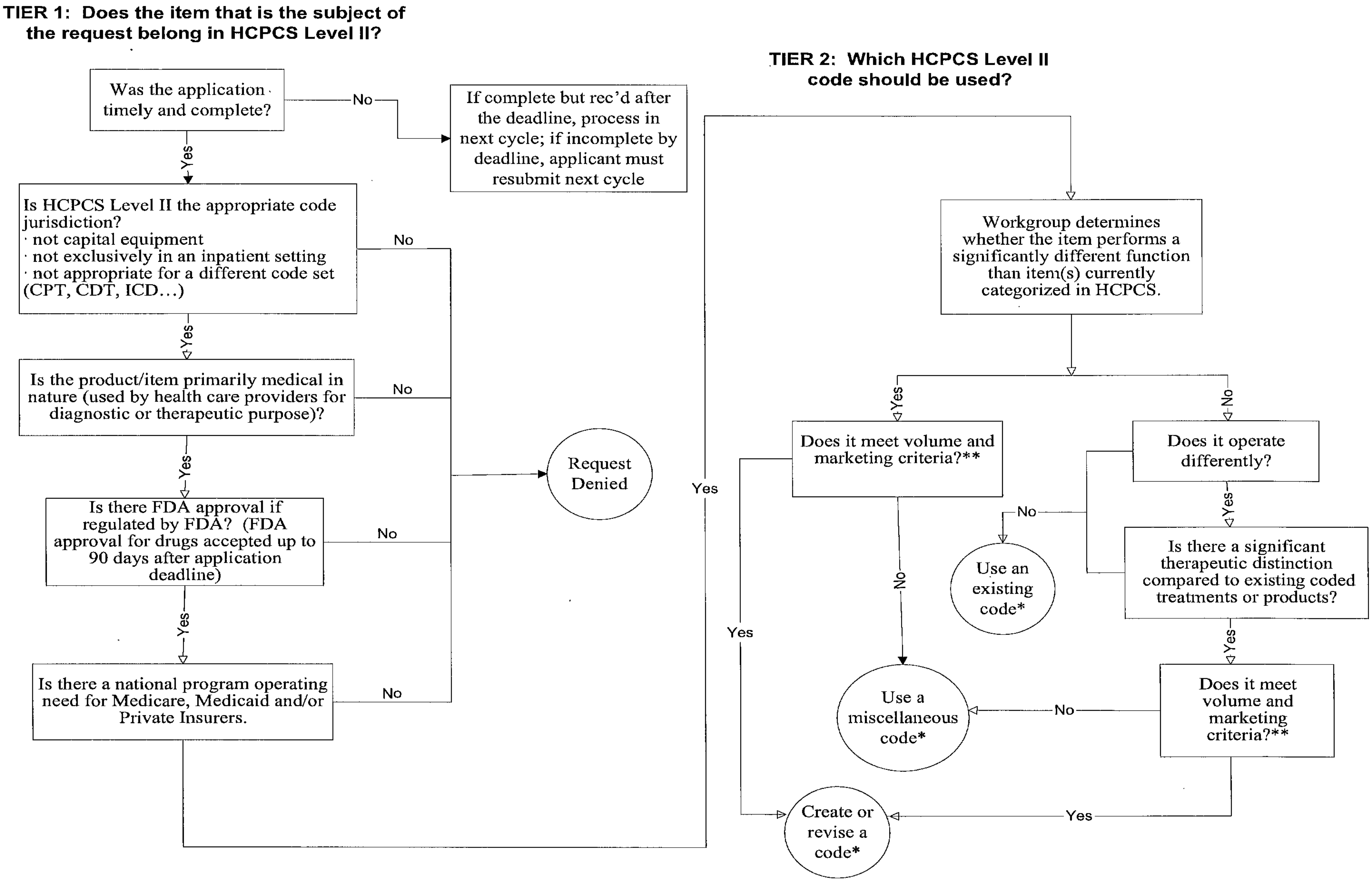
Ex. 40 Proprietary/Privilege Asserted

Ex. 41 Proprietary/Privilege Asserted

Ex. 42 Proprietary/Privilege Asserted

HCPCS Decision Tree

For External Requests to Add or Revise Codes



*Subject to national program operating need

**For drugs, volume and marketing criteria are waived, and "yes" is assumed for the purpose of following the decision tree

Definitions and Clarifications

Tier 1:

HCPCS 2 is the appropriate code jurisdiction: Item is not within the jurisdiction of CPT, CDT, ICD or DRG coding.

Primarily Medical in nature: Item is primarily and customarily used to serve a medical purpose and is not useful in the absence of a medical condition or injury.

FDA approved if regulated: See the online Medicare Benefit Policy Manual #100.2, Chapter 15 – Covered Medical and Other Health Service, Section 50.4.1 – Approved Use of Drug. Does not apply if regulated items are not yet approved. Note: FDA approval for drugs accepted up to 90 days after the application deadline.

National Programmatic Need: At least one insurance sector, public (Medicare or Medicaid) or private (commercial insurers) identified a program operating need to separately identify the item and that need is common across the sector, (i.e., nationally, as opposed to one or a handful of individual insurers or states). Does not apply if item identification is statutorily required.

Tier 2:

Existing or similar code: Describes a similar function to previously coded products

Volume and marketing criteria: There must be sufficient claims activity or volume (3% of affected population), as evidenced by 3 months of marketing activity for non-drug products, so that the adding of a new or modified code enhances the efficiency of the system and justifies the administrative burden of adding or modifying a code and establishing policy and system edits.
Note: Marketing data requirements waived for drugs only.

Performs a different function: Does something completely different to the patient. Examples: suction for a different purpose; static vs. dynamic; swing vs. stance.

Operates differently: Performs the same or similar function to other items, using a different mechanism. Examples: mechanical vs. electronic; automatic vs. manual regulating; extrinsic vs. intrinsic lubrication.

Significant Therapeutic Distinction: Improved medical benefit when compared with the use of other, similar items, e.g., significantly improved medical outcome or significantly superior clinical outcome. Requests for modifications to the HCPCS Level II code set based on such claims are reviewed on a case-by-case basis, taking into consideration clinical information provided by the applicant and other commentators that supports or refutes the claim(s) made by the applicant. In submitting a request, an applicant should provide the best available information supporting his or her claim. Greater weight will be given to more methodologically rigorous and scientifically reliable evidence. Note that process indicators (such as improved compliance, convenience and personal preference) are considered significant distinctions only to the extent that they result in demonstrably improved clinical outcomes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Medicare & Medicaid Services

REVISED product from the Medicare Learning Network® (MLN):

- "Medicare Enrollment and Claim Submission Guidelines", Booklet, ICN 906764, Downloadable and hard copy

MLN Matters® Number: MM8531 Revised

Related Change Request (CR) #: CR 8531

Related CR Release Date: December 13, 2013

Effective Date: January 1, 2014

Related CR Transmittal #: R2836CP

Implementation January 6, 2014

Calendar Year (CY) 2014 Update for Durable Medical Equipment, Prosthetics, Orthotics and Supplies (DMEPOS) Fee Schedule

Note: This article was revised on March 6, 2014, to provide updates regarding HCPCS codes changes that were effective January 1, 2014. The changes are on page 2 (bold). All other information remains unchanged.

Provider Types Affected

This MLN Matters® Article is intended for providers and suppliers submitting claims to Medicare Administrative Contractors (MACs) for DMEPOS items or services paid under the DMEPOS fee schedule.

What You Need to Know

The Centers for Medicare & Medicaid Services (CMS) issued Change Request (CR) 8531 to advise providers of the Calendar Year (CY) 2014 annual update for the Medicare DMEPOS fee schedule. The instructions include information on the data files, update factors, and other information related to the update of the DMEPOS fee schedule. Make sure your staffs are aware of these updates.

Background and Key Points of CR8531

The DMEPOS fee schedules are updated on an annual basis in accordance with statute and regulations. The update process for the DMEPOS fee schedule is located in the "Medicare Claims Processing Manual," Chapter 23, Section 60, which is available at http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/clm104c23.pdf on the CMS website.
Payment on a fee schedule basis is required for Durable Medical Equipment (DME), prosthetic devices, orthotics, prosthetics, and surgical dressings by Section1834 (a), (h), and (i) of the Social Security Act (the Act). Also, payment on a fee schedule basis is a regulatory requirement at 42 CFR Section 414.102 for Parenteral and Enteral Nutrition (PEN) and splints, casts, and certain intraocular lenses.

Fee Schedule Files

The DMEPOS fee schedule file will also be available for providers and suppliers, as well as State Medicaid Agencies, managed care organizations, and other interested parties at http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/DMEPOSFeeSched/ on the CMS website.

Healthcare Common Procedure Coding System (HCPCS) Codes Added/ Deleted

The following new codes are effective January 1, 2014;

- A7047 in the inexpensive/routinely purchased (IN) payment category;
- E0766 in the frequently serviced (FS) payment category; and
  E1352.

The following new codes are in the prosthetics and orthotics (PO) payment category: L5969, L8679, L0455, L0457, L0467, L0469, L0641-L0643, L0648-L0651, L1812, L1833, L1848, L3678, L3809, L3916, L3918, L3924, L3930, L4361, L4387, and L4397.

The following code is deleted from the HCPCS effective January 1, 2014, and therefore, is removed from the DMEPOS fee schedule files: L0430

The following codes are deleted from the DMEPOS fee schedule files as of January 1, 2014: A4611, A4612, A4613, E0457, E0459, L8685, L8686, L8687, and L8688.

For gap-filling purposes, the 2013 deflation factors by payment category are listed in the following table:

Factor	Category
0.469	Oxygen
0.472	Capped Rental
0.473	Prosthetics and Orthotics
0.600	Surgical Dressings
0.653	Parental and Enteral Nutrition

Specific Coding and Pricing Issues

As part of this update, fee schedules for the following codes will be added to the DMEPOS fee schedule file effective January 1, 2014:

- A4387 Ostomy Pouch, Closed, With Barrier Attached, With Built-In Convexity, (I Piece), Each; and
- L3031 Foot, Insert/Plate, Removable, Addition to Lower Extremity Orthotic, High Strength, Lightweight Material, All Hybrid Lamination/Prepreg Composite, Each.

CMS is adjusting the fee schedule amounts for shoe modification codes A5503 through A5507 as part of this update in order to reflect more current allowed service data. Section 1833(o)(2)(C) of the Act required that the payment amounts for shoe modification codes A5503 through A5507 be established in a manner that prevented a net increase in expenditures when substituting these items for therapeutic shoe insert codes,A5512 or A5513. To establish the fee schedule amounts for the shoe modification codes, the base fees for codes A5512 and A5513 were weighted based on the approximated total allowed services for each code for items furnished during the second quarter of CY2004. For 2014, CMS is updating the weighted average insert fees used to establish the fee schedule amounts for the shoe modification codes with more current allowed service data for each insert code. The base fees for A5512 and A5513 will be weighted based on the approximated total allowed services for each code for items furnished during the Calendar Year 2012. The fee schedule amounts for shoe modification codes A5503 through A5507 are being revised to reflect this change, effective January 1, 2014.

Off-the-Shelf Orthotics

Section 1847(a)(2)(C) of the Act mandates implementation of competitive bidding programs throughout the United States for awarding contracts for furnishing Off-The-Shelf (OTS) orthotics which require minimal self-adjustment for appropriate use and do not require expertise in trimming, bending, molding, assembling, or customizing to fit the individual. Regulations at 42 CFR 414.402 define the term “minimal self-adjustment” to mean an adjustment that the beneficiary, caretaker for the beneficiary, or supplier of the device can perform and that does not require the services of a certified orthotist,an individual who is certified by the American Board for Certification in Orthotics and Prosthetics, Inc, or by the Board for Orthotist/Prosthetist Certificationor an individual who has specialized training.

As shown in the following table, 22 new codes are added to the HCPCS for OTS orthotics. In addition, as part of the review to determine which HCPCS codes for prefabricated orthotics describe OTS orthotics, it was determined that HCPCS codes for prefabricated orthotics describe items that are furnished OTS and items that require expertise in customizing the orthotic to fit the individual patient. Therefore, it was necessary to explode these codes into two sets of codes. One set is the existing codes revised, effective January 1, 2014, to only describe devices customized to fit a specific patient by an individual with expertise and a second set of new codes describing the OTS items.

Also, as shown in the table that follows for CY 2014, the fee schedule amounts for existing codes will be applied to the corresponding new codes added for the items furnished OTS. The cross walking of fee schedule amounts for a single code that is exploded into two codes for distinct complete items is in accordance with the instructions found in the "Medicare Claims Processing Manual," Chapter 23,

Section 60.3.1, which is available at http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/clm104c23.pdf on the CMS website.

Prefabricated Orthotic Codes Split into Two Codes—Effective January 1, 2014

Fee from Existing Code	Crosswalk to New Off-The-Shelf and Revised Custom Fitted Orthotic Codes
L0454	L0455 and L0454
L0456	L0457 and L0456
L0466	L0467 and L0466
L0468	L0469 and L0468
L0626	L0641 and L0626
L0627	L0642 and L0627
L0630	L0643 and L0630
L0631	L0648 and L0631
L0633	L0649 and L0633
L0637	L0650 and L0637
L0639	L0651 and L0639
L1810	L1812 and L1810
L1832	L1833 and L1832
L1847	L1848 and L1847
L3807	L3809 and L3807
L3915	L3916 and L3915
L3917	L3918 and L3917
L3923	L3924 and L3923
L3929	L3930 and L3929
L4360	L4361 and L4360
L4386	L4387 and L4386
L4396	L4397 and L4396

Further information on the development of new OTS orthotic codes can be found at http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/DMEPOSFeeSched/OTS_Orthotics.html on the CMS website.

Neurostimulator Devices

HCPCS codes, L8685, L8686, L8687, and L8688 are not included on the 2014 DMEPOS fee schedule file. They were removed from the file to reflect the change in the coverage indicators for these codes to invalid for Medicare ("I") effective January 1, 2014. However, code L8679 (Implantable Neurostimulator, Pulse Generator, Any Type) is added to the HCPCS and DMEPOS fee schedule file, effective January 1, 2014, for billing Medicare claims previously submitted under L8685, L8686, L8687 and L8688. The fee schedule amounts for code L8679 are based on the established Medicare fee schedule amounts for all types of pulse generators under the previous HCPCS code E0756 Implantable Neurostimulator Pulse Generator which was discontinued effective 12/31/2005. The payment amount is based on the explosion of code E0756 into four codes for different types of neurostimulator pulse generator systems which were not materially utilized in the Medicare program. As such, payment for code L8679 will revert back to the fee schedule amounts previously established for code E0756.

Diabetic Testing Supplies

The fee schedule amounts for non-mail order diabetic testing supplies, without KL modifier, for codes A4233, A4234, A4235, A4236, A4253, A4256, A4258, A4259 are not updated by the covered item update for CY 2014. In accordance with Section 636(a) of the American Taxpayer Relief Act of 2012, the fee schedule amounts for these codes were adjusted in CY 2013 so that they are equal to the single payment amounts for mail order Diabetic Testing Supplies (DTS) established in implementing the national mail order Competitive Bidding Program (CBP) under Section 1847 of the Act. The non-mail order payment amounts on the fee schedule file will be updated each time the single payment amounts are updated which can happen no less often than every three years as CBP contracts are recompeted. The national CBP for mail order diabetic supplies is effective July 1, 2013, to June 30, 2016. The program instructions reviewing these changes are Transmittal 2709, Change Request (CR) 8325, dated May 17, 2013, and Transmittal 2661, Change Request (CR) 8204, dated February 22, 2013. You may review the MLN Matters® Articles for these CRs at http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/downloads/MM8325.pdf and http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/downloads/MM8204.pdf on the CMS website.

Although for payment purposes the single payment amounts replace the fee schedule amounts for mail order DTS (KL modifier), the fee schedule amounts remain on the DMEPOS fee schedule file as reference data such as for establishing bid limits for future rounds of competitive bidding programs. The mail order DTS fee schedule amounts shall be updated annually by the covered item update, adjusted for Multi-Factor Productivity (MFP), which results in update of 1.0 percent for CY 2014. The single payment amount public use file for the national mail order competitive bidding program is available

http://www.dmecompetitivebid.com/palmetto/cbicrd2.nsf/DocsCat/Single%20Payment%20Amounts on the Internet.

CY2014 Fee Schedule Update Factor

For CY 2014, the update factor of 1.0 percent is applied to the applicable CY 2013 DMEPOS fee schedule amounts. In accordance with the statutory Sections 1834(a)(14) and 1886(b)(3)(B)(xi)(II) of the Act, the DMEPOS fee schedule amounts are to be updated for 2014 by the percentage increase in the consumer price index for all urban consumers (United States city average) or CPI-U for the 12-month period ending with June of 2013, adjusted by the change in the economy-wide productivity equal to the 10-year moving average of changes in annual economy-wide private non-farm business Multi-Factor Productivity (MFP).

The MFP adjustment is 0.8 percent and the CPI-U percentage increase is 1.8 percent. Thus, the 1.8 percentage increase in the CPI-U is reduced by the 0.8 percentage increase in the MFP resulting in a net increase of 1.0 percent for the update factor.

2014 Update to the Labor Payment Rates

The 2014 fees for HCPCS labor payment codes K0739, L4205, and L7520 are increased 1.8 percent effective for claims with dates of service from January 1, 2014, through December 31, 2014 and those rates are as follows:

STATE	K0739	L4205	L7520
AK	$27.40	$31.22	$36.73
AL	14.55	21.68	29.43
AR	14.55	21.68	29.43
AZ	17.99	21.66	36.21
CA	22.32	35.59	41.48
CO	14.55	21.68	29.43
CT	24.30	22.16	29.43
DC	14.55	21.66	29.43
DE	26.79	21.66	29.43
FL	14.55	21.68	29.43
GA	14.55	21.68	29.43
HI	17.99	31.22	36.73
IA	14.55	21.66	35.23
ID	14.55	21.66	29.43

STATE	K0739	L4205	L7520
NC	14.55	21.68	29.43
ND	18.13	31.16	36.73
NE	14.55	21.66	41.04
NH	15.62	21.66	29.43
NJ	19.63	21.66	29.43
NM	14.55	21.68	29.43
NV	23.18	21.66	40.12
NY	26.79	21.68	29.43
OH	14.55	21.66	29.43
OK	14.55	21.68	29.43
OR	14.55	21.66	42.32
PA	15.62	22.30	29.43
PR	14.55	21.68	29.43
RI	17.34	22.32	29.43

STATE	K0739	L4205	L7520
IL	14.55	21.66	29.43
IN	14.55	21.66	29.43
KS	14.55	21.66	36.73
KY	14.55	27.76	37.64
LA	14.55	21.68	29.43
MA	24.30	21.66	29.43
MD	14.55	21.66	29.43
ME	24.30	21.66	29.43
MI	14.55	21.66	29.43
MN	14.55	21.66	29.43
MO	14.55	21.66	29.43
MS	14.55	21.68	29.43
MT	14.55	21.66	36.73

STATE	K0739	L4205	L7520
SC	$14.55	21.68	29.43
SD	16.26	21.66	39.35
TN	14.55	21.68	29.43
TX	14.55	21.68	29.43
UT	14.59	21.66	45.83
VA	14.55	21.66	29.43
VI	14.55	21.68	29.43
VT	15.62	21.66	29.43
WA	23.18	31.77	37.74
WI	14.55	21.66	29.43
WV	14.55	21.66	29.43
WY	20.28	28.89	41.04

2014 National Monthly Payment Amounts for Stationary Oxygen Equipment

CR8531 implements the 2014 national monthly payment amount for stationary oxygen equipment (HCPCS codes E0424, E0439, E1390, and E1391), effective for claims with dates of service on or after January 1, 2014. As required by statute, the payment amount must be adjusted on an annual basis, as necessary, to ensure budget neutrality of the new payment class for Oxygen Generating Portable Equipment (OGPE). The updated 2014 monthly payment amount of $178.24 includes the 1 percent update factor for the 2014 DMEPOS fee schedule.

Please note that when updating the stationary oxygen equipment fees, corresponding updates are made to the fee schedule amounts for HCPCS codes E1405 and E1406 for oxygen and water vapor enriching systems. Since 1989, the fees for codes E1405 and E1406 have been established based on a combination of the Medicare payment amounts for stationary oxygen equipment and nebulizer codes E0585 and E0570, respectively.

2014 Maintenance and Servicing Payment Amount for Certain Oxygen Equipment

CR8531 also updates the 2014 payment amount for maintenance and servicing for certain oxygen equipment. You can read more about payment for claims for maintenance and servicing for oxygen equipment in MLN Matters® Articles,MM6792 at http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/downloads/MM6792.pdf and MM6990 at http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/downloads/MM6990.pdf on the CMS website.

To summarize, payment for maintenance and servicing of certain oxygen equipment can occur every 6 months beginning 6 months after the end of the 36th month of continuous use or end of the supplier's or manufacturer's warranty, whichever is later for either HCPCS code E1390, E1391, E0433 or K0738, billed with the "MS" modifier. Payment cannot occur more than once per beneficiary, regardless of the combination of oxygen concentrator equipment and/or transfilling equipment used by the beneficiary, for any 6-month period.

Per 42 CFR 414.210(5)(iii), the 2010 maintenance and servicing fee for certain oxygen equipment was based on 10 percent of the average price of an oxygen concentrator. For CY 2011 and subsequent years, the maintenance and servicing fee is adjusted by the covered item update for DME as set forth in Section1834(a)(14) of the Act. Thus, the 2013 maintenance and servicing fee is adjusted by the 1 percent MFP-adjusted covered item update factor to yield a CY 2014 maintenance and servicing fee of $68.73 for oxygen concentrators and transfilling equipment.

Additional Information

The official instruction, CR8531 issued to your MAC regarding this change may be viewed at http://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/Downloads/R2836CP.pdf on the CMS website.

If you have any questions, please contact your MAC at their toll-free number, which may be found at http://www.cms.gov/Research-Statistics-Data-and-Systems/Monitoring-Programs/provider-compliance-interactive-map/index.html on the CMS website.

News Flash - Generally, Medicare Part B covers one flu vaccination and its administration per flu season for beneficiaries without co-pay or deductible. Now is the perfect time to vaccinate beneficiaries. Health care providers are encouraged to get a flu vaccine to help protect themselves from the flu and to keep from spreading it to their family, co-workers, and patients. Note: The flu vaccine is not a Part D-covered drug. For more information, visit:

- MLN Matters® Article #MM8433, "Influenza Vaccine Payment Allowances - Annual Update for 2013-2014 Season"
- MLN Matters® Article #SE1336, "2013-2014 Influenza (Flu) Resources for Health Care Professionals"
- HealthMap Vaccine Finder - a free, online service where users can search for locations offering flu and other adult vaccines. While some providers may offer flu vaccines, those that don't can help their patients locate flu vaccines within their local community.
- The CDC website for Free Resources, including prescription-style tear-pads that allow you to give a customized flu shot reminder to patients at high-risk for complications from the flu.

Excerpt from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Central Nervous System Cancers

Overall management of Central Nervous System Cancers from diagnosis through recurrence is described in the full NCCN Guidelines® for Central Nervous System Cancers. Visit NCCN.org to view the complete library of NCCN Guidelines.

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RECURRENCE | **TREATMENT**

Recurrent disease[s,t] for:
- **Anaplastic oligodendroglioma**
- **Anaplastic oligoastrocytoma**
- **Anaplastic astrocytoma**
- **Anaplastic gliomas**
- **Glioblastoma**

→ **Diffuse or multiple** → **Palliative/Best supportive care if poor performance status or Systemic chemotherapy[k,u] or Surgery for symptomatic,large lesion or Consider alternating electric field therapy (for glioblastoma) (category 2B)[v]**

→ **Local**
- → **Resectable**
  - → **Resection + carmustine (BCNU) wafer[l]** →
  - → **Resection without carmustine (BCNU) wafer** →
- → **Unresectable** →

→ **Palliative/Best supportive care if poor performance status or Systemic chemotherapy[k,u] or Consider reirradiation (category 2B)[j,w] or Consider alternating electric field therapy (for glioblastoma) (category 2B)[v]**

→ **Palliative/Best supportive care**
See NCCN Guidelines for Palliative Care

[a] This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.

[j] See Principles of Brain Tumor Radiation Therapy (BRAIN-C).

[k] See Principles of Brain Tumor Systemic Therapy (BRAIN-D).

[n] Treatment with carmustine wafer, reirradiation, or multiple prior systemic therapies, may impact enrollment in some adjuvant clinical trials.

[s] Consider MR spectroscopy, MR perfusion, or brain PET to rule out radiation necrosis.

[t] Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging. With pseudoprogression, stabilization or improvement should be expected within 3 mo of the end of radiotherapy.

[u] Anaplastic oligodendrogliomas have been reported to be especially sensitive to chemotherapy. Chemotherapy using temozolomide or nitrosourea-based regimens may be appropriate.

[v] Stupp R, Wong ET, Kanner A A, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality. European Journal of Cancer 2012;48:2192-2202.

[w] Especially if long interval since prior RT and/or if there was a good response to prior RT.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Central Nervous System Cancers

Version 1.2016

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GLIOBLASTOMA PATHOLOGY[d]			MGMT[n] PROMOTOR STATUS	ADJUVANT TREATMENT	FOLLOW-UP[b]	
Glioblastoma[j] ± carmustine (BCNU) wafer[o] →	Age ≤70 y →	Good performance status (KPS ≥60) →	Methylated →	Standard brain RT[k] + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy[m,p,q,r] or Standard brain RT[k] + concurrent temozolomide and adjuvant temozolomide (category 1)[m,p,q] →	MRI 2–6 wk after RT, then every 2–4 mo for 2–3 y, then less frequently →	See Recurrence (GLIO-5)
			Unmethylated or indeterminate →	Standard brain RT[k] + concurrent temozolomide[s] and adjuvant temozolomide[s] + alternating electric field therapy[m,p,q,r] or Standard brain RT[k] + concurrent temozolomide[s] and adjuvant temozolomide (category 1)[m,p,q,s] or Standard brain RT alone[k] →	MRI 2–6 wk after RT, then every 2–4 mo for 2–3 y, then less frequently →	See Recurrence (GLIO-5)
		Poor performance status (KPS <60) →		Standard or hypofractionated brain RT[k] or Temozolomide[t] or Palliative/Best supportive care →	MRI 2–6 wk after RT, then every 2–4 mo for 2–3 y, then less frequently →	See Recurrence (GLIO-5)
	Age >70 y →	See GLIO-4				

[a]This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[d]See Principles of Brain Tumor Pathology (BRAIN-F).
[j]This pathway also includes gliosarcoma.
[k]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[m]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[n]MGMT= O^6-methylguanine-DNA methyltransferase.
[o]Treatment with carmustine wafer, reirradiation, or multiple prior systemic therapies may impact enrollment in some adjuvant clinical trials.
[p]Combination of agents may lead to increased toxicity or radiographic changes.
[q]Benefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown. The optimal duration of treatment with temozolomide for anaplastic astrocytoma is unknown.
[r]Alternating electric field therapy is only an option for patients with supratentorial disease.
[s]Clinical benefit from temozolomide is likely to be lower in patients whose tumors lack MGMT promotor methylation.
[t]Temozolomide monotherapy is only recommended if tumor is MGMT promotor methylated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

GLIOBLASTOMA PATHOLOGY[d]		MGMT PROMOTOR STATUS[n]	ADJUVANT TREATMENT	FOLLOW-UP[b]	
Age >70 y (Glioblastoma[j] ± carmustine (BCNU) wafer[o])	Good performance status (KPS ≥60)	Methylated	Temozolomide or Hypofractionated brain RT alone[k] (category 1) or Hypofractionated brain RT[k] + concurrent and adjuvant temozolomide[m,p,q] or Standard RT[k] + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy[m,p,q,r] or Standard RT[k] + concurrent temozolomide and adjuvant temozolomide[m,p,q]	MRI 2–6 wk after RT, then every 2–4 mo for 2–3 y, then less frequently	See Recurrence (GLIO-5)
		Unmethylated or indeterminate	Hypofractionated brain RT alone[k] (category 1) or Standard RT[k] + concurrent temozolomide[s] and adjuvant temozolomide[s] + alternating electric field therapy[m,p,q,r] or Standard RT[k] + concurrent temozolomide[s] and adjuvant temozolomide[m,p,q,s]		
	Poor performance status (KPS <60)		Hypofractionated brain RT alone[k] or Temozolomide[t] or Palliative/Best supportive care		

[a]This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[d]See Principles of Brain Tumor Pathology (BRAIN-F).
[j]This pathway also includes gliosarcoma.
[k]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[m]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[n]MGMT= O^6-methylguanine-DNA methyltransferase.
[o]Treatment with carmustine wafer, reirradiation, or multiple prior systemic therapies may impact enrollment in some adjuvant clinical trials.
[p]Combination of agents may lead to increased toxicity or radiographic changes.
[q]Benefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown. The optimal duration of treatment with temozolomide for anaplastic astrocytoma is unknown.
[r]Alternating electric field therapy is only an option for patients with supratentorial disease.
[s]Clinical benefit from temozolomide is likely to be lower in patients whose tumors lack MGMT promotor methylation.
[t]Temozolomide monotherapy is only recommended if tumor is MGMT promotor methylated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

patients age 70 years or older with mean Karnofsky score of 70 found no survival difference between those receiving RT alone and those taking monthly temozolomide only.[87] Given the susceptibility of elderly patients to RT-induced neurotoxicity, especially when the PS is poor, chemotherapy alone appears to be a reasonable option.

Combination Chemoradiation

Improved survival observed in 2 randomized clinical trials established combined PCV chemotherapy and RT as the new standard for treating patients with pure or mixed anaplastic oligodendroglioma harboring the 1p/19q co-deletion. RTOG 9402 randomized 291 patients to PCV followed by immediate RT or RT alone.[88] No difference was observed between the two arms for the entire cohort. However, an unplanned analysis showed that patients with the co-deletion lived longer than those without, and among patients with co-deleted tumors, median survival was doubled when PCV was added to RT (14.7 vs. 7.3 years; HR, 0.59; 95% CI, 0.37–0.95; $P = .03$). This difference was not observed for patients without 1p/19q co-deletion.

Similarly, EORTC 26951 randomly assigned 368 patients with pure or mixed anaplastic oligodendroglioma to RT or RT followed by PCV.[89] At a median follow-up of 140 months, overall survival was longer in the combination arm than in the RT arm (42.3 vs. 30.6 months; HR, 0.75; 95% CI, 0.60–0.95). Median survival was not reached in patients with co-deleted tumors who received PCV/RT compared to 112 months for those in the RT group. No survival advantage was found with the addition of PCV among patients without the co-deletion.

Systemic Therapy for Recurrence

Unfortunately, currently available chemotherapy does not provide cures. Patients with malignant gliomas eventually recur or progress. In addition to temozolomide[36,90,91] and nitrosoureas,[71,92] regimens that are commonly used as second-line chemotherapy include combination PCV,[93] cyclophosphamide (category 2B recommendation),[94,95] and platinum-based regimens (category 2B recommendation).[39] Anaplastic gliomas may also be treated by irinotecan[96] or etoposide.[97]

Bevacizumab, an anti-angiogenic agent, received accelerated approval in 2009 for recurrent glioblastoma based on two phase II studies. AVF 3708g randomized 167 patients to bevacizumab with or without irinotecan. MRI-defined objective response was achieved in 28% and 38% of patients, respectively.[98] Median survival was around 9 months, similar to that of a previous phase II trial.[99] A published report of the other pivotal study (NCI 06-C-0064E) recorded a median survival of 31 weeks in 48 heavily pretreated patients.[100] In the case that patients with good PS who have received bevacizumab monotherapy showed signs of radiographic progression, continuation of bevacizumab therapy may prevent rapid neurologic deterioration. Bevacizumab in combination with irinotecan, carmustine or lomustine, carboplatin (category 2B) or temozolomide has also been used in anaplastic gliomas.[101-108] These combinations may be considered for patients who have failed bevacizumab monotherapy. While efficacious, bevacizumab is associated with potentially serious adverse events including hypertension, impaired wound healing, colonic perforation, and thromboembolism.

Alternating Electric Field Therapy

In 2011, the FDA approved a portable medical device that generates low-intensity electric fields termed Tumor Treating Fields (TTF) for the treatment of recurrent glioblastoma. Approval was based on results of a clinical trial that randomized 237 patients to TTF or chemotherapy.[109] Similar survival was observed in the two arms, and TTF therapy was associated with lower toxicity and improved quality of life. Due to the lack of efficacy, not all panelists recommended the treatment.

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RADIOLOGIC PRESENTATION[b]		CLINICAL IMPRESSION	SURGERY[c]		PATHOLOGY[d]	
MRI suggestive of high-grade glioma[e,f] →	Multidisciplinary input for treatment planning if feasible →	Maximal safe resection feasible with goal for image-verified complete resection →	Maximal safe resection ± carmustine (BCNU) wafer[g,h] (category 2B) →	Brain MRI[b,i] →	• Anaplastic oligodendroglioma • Anaplastic oligoastrocytoma[k] • Anaplastic astrocytoma • Anaplastic gliomas →	See Adjuvant Treatment (GLIO-2)
		Maximal safe resection not feasible →	Stereotactic biopsy or Open biopsy or Subtotal resection (MRI after resection)[i] →		Glioblastoma[j] →	See Adjuvant Treatment (GLIO-3)

[a]This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[c]See Principles of Brain Tumor Surgery (BRAIN-B).
[d]See Principles of Brain Tumor Pathology (BRAIN-F).
[e]Biopsy first if MRI compatible with CNS lymphoma.
[f]Consider a multidisciplinary review in treatment planning, especially once pathology is available (See Principles of Brain Tumor Management [BRAIN-E]).
[g]If frozen section diagnosis supports high-grade glioma.
[h]Treatment with carmustine wafer may impact enrollment in some adjuvant clinical trials.
[i]Postoperative brain MRI within 24–72 hours after surgery.
[j]This pathway also includes gliosarcoma.
[k]NOS WHO 2016 has deleted this category, although it may continue to be used for some patients.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ANAPLASTIC GLIOMAS
(See GLIO-3/GLIO-4 for GBM)

PATHOLOGY[d]	ADJUVANT TREATMENT	FOLLOW-UP[b]	
Anaplastic oligodendroglioma (1p19q codeleted) →	Fractionated external beam RT[l] and neoadjuvant or adjuvant[m] PCV chemotherapy (category 1)[n] or Fractionated external beam RT[l] with concurrent and adjuvant temozolomide chemotherapy[n]	→ Brain MRI 2–6 wks after RT, then every 2–4 mo for 3 y, then every 6 months indefinitely[o]	→ See Recurrence (GLIO-5)
Anaplastic astrocytoma Anaplastic oligoastrocytoma[k] →	Fractionated external beam RT[l] with concurrent and adjuvant temozolomide chemotherapy[n] or Fractionated external beam RT[l] + neoadjuvant or adjuvant[m] PCV or Fractionated external beam RT[l]	→ Brain MRI 2–6 wks after RT, then every 2–4 mo for 3 y, then every 6 months indefinitely[o]	→ See Recurrence (GLIO-5)
Anaplastic gliomas[a] Poor performance status (KPS <60) →	Fractionated external beam RT[l] (hypofractionated [preferred] or standard) or PCV or temozolomide chemotherapy (category 2B)[n] or Palliative/Best supportive care	→ Brain MRI 2–6 wks after RT, then every 2–4 mo for 3 y, then every 6 months indefinitely[o]	→ See Recurrence (GLIO-5)

[a]This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[d]See Principles of Brain Tumor Pathology (BRAIN-F).
[k]NOS WHO 2016 has deleted this category, although it may continue to be used for some patients.
[l]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[m]The panel recommends that PCV be administered after RT (as per EORTC 26951) since the intensive PCV regimen given prior to RT (RTOG 9402) was not tolerated as well.
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[o]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.

EB-1

All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Anaplastic Gliomas[a]/Glioblastoma

NCCN Evidence Blocks™

NCCN Guidelines Index
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Discussion

GLIOBLASTOMA PATHOLOGY[d]			MGMT[p] PROMOTER STATUS	ADJUVANT TREATMENT	FOLLOW-UP[b]	
Glioblastoma[j] ± carmustine (BCNU) wafer[q]	Age ≤70 y	Good performance status (KPS ≥60)	Methylated	Standard brain RT[l] + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy[n,r,s,t] or Standard brain RT[l] + concurrent temozolomide and adjuvant temozolomide (category 1)[n,r,s]	Brain MRI 2–6 wk after RT, then every 2–4 mo for 3 y, then every 6 mo indefinitely[o]	See Recurrence (GLIO-5)
			Unmethylated or indeterminate	Standard brain RT[l] + concurrent temozolomide[u] and adjuvant temozolomide[u] + alternating electric field therapy[n,r,s,t] or Standard brain RT[l] + concurrent temozolomide[u] and adjuvant temozolomide (category 1)[n,r,s,u] or Standard brain RT alone[l]		
		Poor performance status (KPS <60)		Standard or hypofractionated brain RT[l] or Temozolomide[v] or Palliative/Best supportive care		
	Age >70 y	See GLIO-4				

See Evidence Blocks on BRAIN-D (EB-3)

[a]This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[d]See Principles of Brain Tumor Pathology (BRAIN-F).
[j]This pathway also includes gliosarcoma.
[l]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[o]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.
[p]MGMT= O^6-methylguanine-DNA methyltransferase.
[q]Treatment with carmustine wafer, reirradiation, or multiple prior systemic therapies may impact enrollment in some adjuvant clinical trials.
[r]Combination of agents may lead to increased toxicity or radiographic changes.
[s]Benefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown. The optimal duration of treatment with temozolomide for anaplastic astrocytoma is unknown.
[t]Alternating electric field therapy is only an option for patients with supratentorial disease.
[u]Clinical benefit from temozolomide is likely to be lower in patients whose tumors lack MGMT promoter methylation.
[v]Temozolomide monotherapy is only recommended if tumor is MGMT promoter methylated.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

GLIOBLASTOMA PATHOLOGY[d] | **MGMT PROMOTER STATUS[p]** | **ADJUVANT TREATMENT** | **FOLLOW-UP[b]**

Age >70 y (Glioblastoma[j] ± carmustine [BCNU] wafer[q])

- Good performance status (KPS ≥60)
  - Methylated →
    - Hypofractionated brain RT[l] + concurrent and adjuvant temozolomide[n,r,s]
    - or Temozolomide
    - or Hypofractionated brain RT alone[l] (category 1)
    - or Standard RT[l] + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy[n,r,s,t]
    - or Standard RT[l] + concurrent temozolomide and adjuvant temozolomide[n,r,s]
  - Unmethylated or indeterminate →
    - Hypofractionated brain RT alone[l] (category 1)
    - or Standard RT[l] + concurrent temozolomide[u] and adjuvant temozolomide[u] + alternating electric field therapy[n,r,s,t]
    - or Standard RT[l] + concurrent temozolomide[u] and adjuvant temozolomide[n,r,s,u]
- Poor performance status (KPS <60) →
  - Hypofractionated brain RT alone[l]
  - or Temozolomide[v]
  - or Palliative/Best supportive care

→ Brain MRI 2–6 wk after RT, then every 2–4 mo for 3 y, then every 6 mo through 5 y post-treatment, then yearly indefinitely[o] → See Recurrence (GLIO-5)

[a]This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[d]See Principles of Brain Tumor Pathology (BRAIN-F).
[j]This pathway also includes gliosarcoma.
[l]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[o]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.
[p]MGMT= O^6-methylguanine-DNA methyltransferase.
[q]Treatment with carmustine wafer, reirradiation, or multiple prior systemic therapies may impact enrollment in some adjuvant clinical trials.
[r]Combination of agents may lead to increased toxicity or radiographic changes.
[s]Benefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown. The optimal duration of treatment with temozolomide for anaplastic astrocytoma is unknown.
[t]Alternating electric field therapy is only an option for patients with supratentorial disease.
[u]Clinical benefit from temozolomide is likely to be lower in patients whose tumors lack MGMT promoter methylation.
[v]Temozolomide monotherapy is only recommended if tumor is MGMT promoter methylated.

EB-1.
All recommendations are category 2A unless otherwise indicated.
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patients age 70 years or older with mean Karnofsky score of 70 found no survival difference between those receiving RT alone and those taking monthly temozolomide only.[87] Given the susceptibility of elderly patients to RT-induced neurotoxicity, especially when the PS is poor, chemotherapy alone appears to be a reasonable option.

Combination Chemoradiation

Improved survival observed in 2 randomized clinical trials established combined PCV chemotherapy and RT as the new standard for treating patients with pure or mixed anaplastic oligodendroglioma harboring the 1p/19q co-deletion. RTOG 9402 randomized 291 patients to PCV followed by immediate RT or RT alone.[88] No difference was observed between the two arms for the entire cohort. However, an unplanned analysis showed that patients with the co-deletion lived longer than those without, and among patients with co-deleted tumors, median survival was doubled when PCV was added to RT (14.7 vs. 7.3 years; HR, 0.59; 95% CI, 0.37–0.95; P = .03). This difference was not observed for patients without 1p/19q co-deletion.

Similarly, EORTC 26951 randomly assigned 368 patients with pure or mixed anaplastic oligodendroglioma to RT or RT followed by PCV.[89] At a median follow-up of 140 months, overall survival was longer in the combination arm than in the RT arm (42.3 vs. 30.6 months; HR, 0.75; 95% CI, 0.60–0.95). Median survival was not reached in patients with co-deleted tumors who received PCV/RT compared to 112 months for those in the RT group. No survival advantage was found with the addition of PCV among patients without the co-deletion.

Systemic Therapy for Recurrence

Unfortunately, currently available chemotherapy does not provide cures. Patients with malignant gliomas eventually recur or progress. In addition to temozolomide[36,90,91] and nitrosoureas,[71,92] regimens that are commonly used as second-line chemotherapy include combination PCV,[93] cyclophosphamide (category 2B recommendation),[94,95] and platinum-based regimens (category 2B recommendation).[39] Anaplastic gliomas may also be treated by irinotecan[96] or etoposide.[97]

Bevacizumab, an anti-angiogenic agent, received accelerated approval in 2009 for recurrent glioblastoma based on two phase II studies. AVF 3708g randomized 167 patients to bevacizumab with or without irinotecan. MRI-defined objective response was achieved in 28% and 38% of patients, respectively.[98] Median survival was around 9 months, similar to that of a previous phase II trial.[99] A published report of the other pivotal study (NCI 06-C-0064E) recorded a median survival of 31 weeks in 48 heavily pretreated patients.[100] In the case that patients with good PS who have received bevacizumab monotherapy showed signs of radiographic progression, continuation of bevacizumab therapy may prevent rapid neurologic deterioration. Bevacizumab in combination with irinotecan, carmustine or lomustine, carboplatin (category 2B) or temozolomide has also been used in anaplastic gliomas.[101-108] These combinations may be considered for patients who have failed bevacizumab monotherapy. While efficacious, bevacizumab is associated with potentially serious adverse events including hypertension, impaired wound healing, colonic perforation, and thromboembolism.

Alternating Electric Field Therapy

In 2011, the FDA approved a portable medical device that generates low-intensity electric fields termed Tumor Treating Fields (TTF) for the treatment of recurrent glioblastoma. Approval was based on results of a clinical trial that randomized 237 patients to TTF or chemotherapy.[109] Similar survival was observed in the two arms, and TTF therapy was associated with lower toxicity and improved quality of life. Due to the lack of efficacy, not all panelists recommended the treatment.

NCCN Clinical Practice Guidelines in Oncology
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Central Nervous System Cancers

Overall management of Central Nervous System Cancers from diagnosis through recurrence is described in the full NCCN Guidelines® for Central Nervous System Cancers. Visit NCCN.org to view the complete library of NCCN Guidelines.

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Anaplastic Gliomas[a]/Glioblastoma

GLIOBLASTOMA PATHOLOGY[d] → **MGMT[q] PROMOTER STATUS** → **ADJUVANT TREATMENT** → **FOLLOW-UP[b]**

Glioblastoma[j]

- **Age ≤70 y**
  - **Good performance status (KPS ≥60)**
    - **Methylated** →
      - Consider clinical trial (preferred for eligible patients)
      - or
      - Standard brain RT[l] + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy (category 1)[n,r,s,t]
      - or
      - Standard brain RT[l] + concurrent temozolomide and adjuvant temozolomide (category 1)[n,r,s]
    - **Unmethylated or indeterminate** →
      - Consider clinical trial (preferred for eligible patients)
      - or
      - Standard brain RT[l] + concurrent temozolomide[u] and adjuvant temozolomide[u] + alternating electric field therapy (category 1)[n,r,s,t]
      - or
      - Standard brain RT[l] + concurrent temozolomide[u] and adjuvant temozolomide (category 1)[n,r,s,u]
      - or
      - Standard brain RT alone[l]
  - **Poor performance status (KPS <60)** →
    - Hypofractionated brain RT[l] (preferred) ± concurrent or adjuvant TMZ
    - or
    - Temozolomide[o]
    - or
    - Palliative/Best supportive care
- **Age >70 y** → See GLIO-4

Follow-up (all adjuvant treatment branches) → Brain MRI 2–6 wk after RT,[p] then every 2–4 mo for 3 y, then every 6 mo indefinitely → See Recurrence (GLIO-5)

[a]This pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[d]See Principles of Brain Tumor Pathology (BRAIN-F).
[j]This pathway also includes gliosarcoma.
[l]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[o]Consider temozolomide if tumor is MGMT promoter methylated.
[p]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.
[q] MGMT= O[6]-methylguanine-DNA methyltransferase.
[r]Combination of agents may lead to increased toxicity or radiographic changes.
[s]Benefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown
[t] patients with supratentorial disease.
[u] patients whose tumors lack MGMT promoter methylation.

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GLIO-3

Anaplastic Gliomas[a]/Glioblastoma

GLIOBLASTOMA PATHOLOGY[d]		MGMT PROMOTER STATUS[q]	ADJUVANT TREATMENT	FOLLOW-UP[b]	
Age >70 y Glioblastoma[j]	Good performance status (KPS ≥60)	Methylated →	Consider clinical trial (preferred for eligible patients) or Hypofractionated brain RT[l] + concurrent and adjuvant temozolomide (category 1)[n,r,s] or Standard RT[l] + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy (category 1)[n,r,s,t] or Standard RT[l] + concurrent temozolomide and adjuvant temozolomide[n,r,s] or Temozolomide or Hypofractionated brain RT alone[l]	→ Brain MRI 2–6 wk after RT,[p] then every 2–4 mo for 3 y, then every 6 mo indefinitely	→ See Recurrence (GLIO-5)
		Unmethylated or indeterminate →	Consider clinical trial (preferred for eligible patients) or Hypofractionated brain RT[l] + concurrent and adjuvant temozolomide[n,r,s] or Standard RT[l] + concurrent temozolomide[u] and adjuvant temozolomide[u] + alternating electric field therapy (category 1)[n,r,s,t] or Standard RT[l] + concurrent temozolomide[u] and adjuvant temozolomide[n,r,s,u] or Hypofractionated brain RT alone[l]		
	Poor performance status (KPS <60) →		Hypofractionated brain RT alone[l] or Temozolomide[o] or Palliative/Best supportive care →		

See footnotes on GLIO-4A

All recommendations are category 2A unless otherwise indicated.
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OPT-1511

GL-N-0834-0718

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Room –WO66-G609
Silver Spring, MD 20993-0002

NovoCure, Ltd.
% Mr. Jonathan S. Kahan
Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, N.W.
Washington, D.C. 20004

APR 8 2011

Re: P100034
NovoTTF-100A System
Filed: August 16, 2010
Amended: September 10, October 19, December 13, and December 27, 2011; and February 17, and April 8, 2011
Procode: NZK

Dear Mr. Kahan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the NovoTTF-100A System. This device is indicated for treatment of adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme, following histologically- or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the conditions outline above, you must conduct the following post-approval study (PAS):

The New Enrollment Study for NovoTTF-100A in Recurrent GBM Patients: Per agreed on study outline (e-mail dated April 5, 2011) this study will address the following question: Is the overall survival of patients treated with NovoTTF-100A non-inferior to the survival of patients treated with the best standard of care (chemotherapy)? This question will be addressed with a prospective, multi-center, non-randomized, unblinded, concurrent control study of NovoTTF-100A in recurrent Glioblastoma Multiforme (GBM) patients. The study will be conducted in at least 30 sites, at least half of them in the United States, and may include centers with previous experience with the device. Patients 22 years old and older will be included in the PAS. A total of 486 subjects will be enrolled, with 243 subjects per study arm. All study participants will be followed until death. Study follow-up visits include baseline and monthly in-office visits until disease progression. Assessment at baseline includes the Mini Mental State Examination (MMSE) and genetic profiling. The monthly assessments include survival status, MMSE and adverse events assessment. After disease progression study participants will be followed by monthly phone calls to determine survival status.

The primary data analysis will compare overall survival in NovoTTF-100A patients to that seen in concurrent BSC comparison patients, in the investigational device exemption (IDE) study Intent-to-Treat population, within a predefined confidence interval bound consistent with a performance goal of 1.375. The secondary endpoints will be: Change in neuro-cognitive function from baseline based on the MMSE; Genetic profiling of tumors and correlation with response to NovoTTF-100A treatment, specifically:

- MGMT promoter methylation status
- EGFR amplification, over expression or rearrangement
- Chromosomes 1p/19q deletion status
- Adverse event incidence by body system and term, including:
- Incidence of seizures
- Anticonvulsant use

Please be advised that the results from these studies should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement.

In addition to the Annual Report requirements, FDA would like to remind you that you are required to submit PAS Progress Reports every six months during the first two years and annually thereafter. The reports should clearly be identified as Post-Approval Study Report. Two copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA.

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a complete protocol of your post-approval study. Your PMA supplement should be clearly labeled as a "Post-Approval Study Protocol" and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm#2

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing. One of those three copies may be an electronic copy (eCopy), in an electronic format that FDA can process, review and archive (general information: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.htm; clinical and statistical data: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm136377.htm)

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Mail Center -- WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Ms. Jan C. Callaway at 301-796-5620.

Sincerely yours,

Mark C. Fisher MD PhD for

Christy Foreman
Acting Director
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

October 05, 2015

Novocure, Ltd.
℅ Mr. Jonathan S. Kahan
Partner
Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004

Re: P100034/S013
Trade/Device Name: Optune™ (Formerly the NovoTTF-100A System)
Filed: April 10, 2015
Amended: July 23, 2015
Product Code: NZK

Dear Mr. Jonathan S. Kahan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement for the Optune™ (formerly the NovoTTF-100A System). This device is indicated as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy. Optune™ was previously approved in 2011 for the treatment of recurrent GBM with the following Indications for Use (IFU): Optune™ is indicated following histologically-or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted. We are pleased to inform you that the PMA supplement is approved. You may begin commercial distribution of the device as modified in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is

therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84. This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final UDI rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. For more information on these requirements, please see the UDI website, http://www.fda.gov/udi.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at http://www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in 6 copies, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Daryl Kaufman at 301-796-6467 or Daryl.Kaufman@fda.hhs.gov.

Sincerely yours,

Carlos L. Pena -S

Carlos L. Peña, PhD, MS
Director
Division of Neurological
and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Central Nervous System
Live SA-CME

Friday, March 2, 2018

10:00 a.m. – 11:30 a.m.

Adult CNS Tumors

SA-CME

Lia M. Halasz, M.D.
Associate Professor and Residency Program Director
Departments of Radiation Oncology and Neurological Surgery
University of Washington

Faculty Disclosures

Faculty and Committee disclosures are also on the 2018 ASTRO Annual Refresher Course website.

Name	Employment	Funding Sources	Ownership or Investments	Leadership
Lia Halasz, MD,	University of Washington	**Fred Hutch/University of Washington Cancer Consortium:** Research Grants	None	None

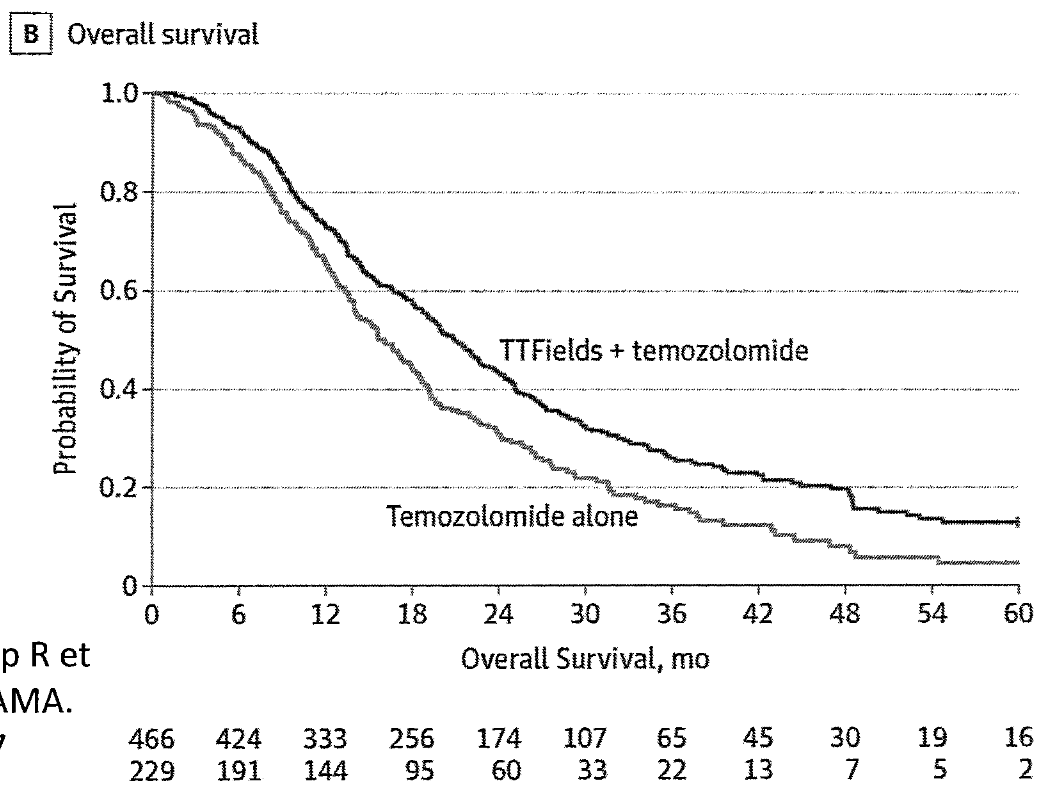
New trial data from 2017-2018

Gliomas:
EORTC/NCIC elderly: 40 Gy in 15 with TMZ
EF-14: TTfields improve overall survival for GBM
CATNON interim report: Adjuvant TMZ for AA

Brain metastases:
NCCTG N107C/CEC.3: After resection, WBRT better local control but same OS as SRS
MDACC: SRS to resection bed improves local control

Meningiomas:
RTOG 0539: Good local control for atypical meningiomas treated with GTR + RT

Tumor-Treating Fields



Stupp R et al. JAMA. 2017

- KPS ≥ 70; median age 56
- Randomized 2:1 after 60 Gy/TMZ
  - Adjuvant TMZ + TTFields
  - Adjuvant TMZ
- Improved median survival (from time of randomization)
  - 16.0 → 20.9 months
  - P<0.001
- Toxicity
  - Skin toxicity in 52%

Histology/ Grade	Molecular Type	My treatment	Median OS	Trial	Notes
G2 Astro	IDH mutant, 1p19q intact, ATRX loss, p53 mutant	54 Gy with CTV margin 1 cm → chemo	6+	RTOG 9802	PCV benefit for IDH mutants; unclear for grade II how TMZ compares to PCV
G3 Astro		59.4 Gy with CTV margin 1.5 cm/TMZ → TMZ	5+	RTOG 9402	
G2 Oligo	IDH mutant, 1p19q codel, ATRX retained, p53 wt	54 Gy with CTV margin 1 cm → PCV	14+	RTOG 9802	Grade 2 and 3 are likely similar prognosis; unclear if TMZ will work as well
G3 Oligo		54 Gy with CTV margin 1.5 cm and boost enhancing disease to 59.4 Gy→ PCV	14+	RTOG 9402 EORTC26951	
G2/3 Provisional	IDH wt	59.4 Gy with CTV margin 1.5 cm/TMZ → TMZ	~2+	RTOG9402 RTOG 9802 RTOG 0424	Unclear how to treat these currently but no poor prognosis
G4	IDH wt or mutated	46 Gy with CTV margin 1.5 cm on FLAIR then 60 Gy with CTV margin 1.5 cm on enhancement/TMZ → TMZ (+TTF)	1-2	EORTC/NCIC EF-14	TTF often not adopted by patients; hypofractionated for elderly

SCIENCE TIMES

A Shock to the System: Tumor-Treating Fields Plus Temozolomide for Glioblastoma

Glioblastoma continues to be a uniformly fatal disease despite decades of aggressive research. Newly diagnosed adult patients continue to face 15% and 4.3% 2- and 5-yr survival rates, respectively.[1] Current standard of care consists of upfront maximal safe resection (or biopsy for diffuse and unresectable lesions) followed by radiotherapy, with concomitant oral temozolomide (TMZ) chemotherapy, with 6 to 12 mo of maintenance TMZ thereafter. With this approach, modern trials have demonstrated overall survival from time of diagnosis of 14.6 to 16.7 mo.[2] Tumor-treating fields (TTFields) have emerged as a novel nonpharmacologic adjunct that has shown promise in preclinical and clinical trials. TTFields work by delivering low-intensity alternating electric fields via a noninvasive scalp mounted transducer array. TTFields therapeutic effect results from arresting mitosis and inducing apoptosis in rapidly dividing cells resulting in increased sensitivity to chemotherapy.[3] Stupp and colleagues[4] previously presented an interim analysis of a phase 3 randomized clinical trial of TTFields plus TMZ versus TMZ alone in newly diagnosed glioblastoma with promising results. They now report in JAMA the final analysis with a median follow up of 40 mo.[5]

The authors designed a multicenter, international, open-label randomized clinical phase 3 trial with centers in North America, Europe, Korea, and Israel. The study population included patients >18 yr old with Karnofsky performance scores (KPS) >70 and newly diagnosed, histologically confirmed supratentorial glioblastoma who were randomized in a 2:1 ratio between TFField plus TMZ and TMZ maintenance therapy alone. Patients with rapid radiographic progression following standard radiochemotherapy, infratentorial tumor location, and severe comorbidities were excluded from enrollment. A total of 695 patients were enrolled in 83 centers and randomized with stratification by extent of resection and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status. The primary end point was progression-free survival with a secondary end point of overall survival conducted in an intent-to-treat manner. Twenty-six patients in the control group crossed over to undergo TTField therapy following the publication of the interim analysis and included in the control group as randomized.

Baseline characteristics between experimental and control groups were well balanced with a median follow-up of 40 mo and a minimum follow up of 24 mo. Median progression-free survival was 6.7 mo in the experimental group versus 4.0 mo in the control group with a Hazard ratio of 0.63. Median survival duration from randomization was 20.9 mo versus 16.0 mo with a Hazard ratio of 0.63 for the experimental and control groups respectively. At 2-, 3-, and 5- yr following randomization 43%, 26%, and 13% of patients were alive in the experimental group compared to 31%, 16%, and 5% in the control group. Between group findings remained consistent when adjusted for KPS, age, MGMT promoter methylation status, geographic region, tumor location, and extent of resection. Patients that lacked MGMT promoter methylation had significantly shorter survival in both groups, though the use of TTFields plus TMZ was associated with improved survival regardless of promoter methylation. No statistically significant difference in adverse events was noted between groups, with the exception of localized skin toxicity in the experimental group. Mild skin irritation occurred in 52% of patients and severe skin involvement in 2%.

This randomized phase 3 clinical trial provides an important addition to the care of patients afflicted with glioblastoma. Based on the strength of the evidence, the addition of TTFields to radiochemotherapy may emerge as the standard of care for newly diagnosed and recurrent glioblastoma patients. Some criticism has emerged regarding the decision to calculate survival data from randomization rather than diagnosis, but when the data were adjusted for this decision, the survival benefit remains robust and significant. Additionally the control group was not truly blinded, as for ethical and practical reasons a sham device was not employed, thus potentially contributing to a placebo effect. Factors that may impact the adoption of TTF therapy include patient tolerability of the device and insurance coverage of the expense. While the need to wear the scalp-mounted transducer array for >18 h a day may appear onerous, 75% of patients in this trial were able to achieve 75% adherence, suggesting good tolerability. From a neurosurgical standpoint, current rates of skin complications may become clinically significant for wound healing purposes if the technology is more widely adapted. Further technological refinement may ultimately lead to improved tolerability and decreased rates of localized skin complications. TTFields in addition to standard of care radiation and chemotherapy provides a valuable new adjunct in the care of patients with glioblastoma.

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frontiers in Pharmacology

REVIEW
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Check for updates

Glioblastoma Treatments: An Account of Recent Industrial Developments

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The different drugs and medical devices, which are commercialized or under industrial development for glioblastoma treatment, are reviewed. Their different modes of action are analyzed with a distinction being made between the effects of radiation, the targeting of specific parts of glioma cells, and immunotherapy. Most of them are still at a too early stage of development to firmly conclude about their efficacy. Optune, which triggers antitumor activity by blocking the mitosis of glioma cells under the application of an alternating electric field, seems to be the only recently developed therapy with some efficacy reported on a large number of GBM patients. The need for early GBM diagnosis is emphasized since it could enable the treatment of GBM tumors of small sizes, possibly easier to eradicate than larger tumors. Ways to improve clinical protocols by strengthening preclinical studies using of a broader range of different animal and tumor models are also underlined. Issues related with efficient drug delivery and crossing of blood brain barrier are discussed. Finally societal and economic aspects are described with a presentation of the orphan drug status that can accelerate the development of GBM therapies, patents protecting various GBM treatments, the different actors tackling GBM disease, the cost of GBM treatments, GBM market figures, and a financial analysis of the different companies involved in the development of GBM therapies.

Keywords: brain cancer, industry, drug development, market, preclinical model

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INTRODUCTION

Glioblastoma multiform (GBM) is a malignant tumor originating from glial cells. It is the most frequent brain tumor, representing 30% of all central nervous system tumors (CNST), 45% of malignant CNST and 80% of primary malignant CNST. It leads to 225,000 deaths per year in the entire word. It has an incidence of 5 per 100,000 persons, affects 1.5 times more men than women, and is diagnosed at an average age of 64 (Bush et al., 2017). Due to the relatively limited number of people suffering from GBM, it is difficult to determine with certainty the causes of this disease. The only well-established GBM risk factor is exposure to radiation. Radiofrequency electromagnetic fields such as those produced by mobile phones have been classified as IIB and may also play a role in GBM appearance (Armstrong et al., 2011). By contrast to other types of cancers, it appears uncertain that GBM incidence can be decreased by changing certain environmental factors such as alcohol or tobacco consumption. Since the majority of GBM appear for the first time, i.e., only ~40% originates from tumors of lower grades, it also seems rather uneasy to anticipate GBM from the presence of another disease or condition.

Among the four different forms of glioma, grade IV corresponds to GBM. It is the most deadly grade, due to its frequent relapse and resistance to all current therapies and is the topic of this review. GBM current standard of care (SOC) includes maximal safe resection followed by radiotherapy and chemotherapy using temozolomide (TMZ). Such treatment hardly increases patient survival and leads to a median overall survival (OS) of only 12–18 months following diagnosis (Stupp et al., 2005; Wen and Kesari, 2008).

Efficient treatment against GBM is difficult to develop for a series of reasons that are summarized below. First, GBM is characterized by many dysregulated pathways that can hardly be all blocked and repaired at the same time with a single therapy (Alifieris and Trafalis, 2015). Second, GBM partly consists of infiltrating cells that cannot easily be all removed by surgery. Full tumor resection would require very precise imaging and surgical tools to enable the visualization and removal of all GBM infiltrating cells. Third, GBM early diagnosis, which may improve treatment efficacy by enabling the removal of tumors of small sizes, is not carried out routinely. In fact, the first signs of GBM, such as vomiting and strong headache, often appear at a late stage of this disease, and sensitive imaging techniques, such as MRI, which could possibly enable early diagnosis, still seem too expensive to be carried out on a regular basis over the whole population. Fourth, the optimization of a clinical protocol for GBM treatment requires the use of an accurate and representative preclinical GBM model. Different types of mouse and rats models have been developed, each one with its own advantages and drawbacks. It therefore appears necessary to test GBM drug efficacy on a combination of several of these models to grasp sufficient information for optimal design of the clinical protocol. Furthermore, mouse and rats GBM tumors are typically $\sim 10^3$-10^4 smaller than human GBM. The optimization of the clinical protocol would therefore certainly benefit from preclinical efficacy tests carried out on larger animals such as dogs. Fifth, the blood brain barrier (BBB) often prevents drugs from efficiently reaching glioblastoma cells, and methods to enable drugs to efficiently cross the BBB should therefore be developed.

Here, I review the different drugs and medical devices, which are under development or commercialized by companies, have been pre-clinically or clinically tested, most frequently involve medical teams, and either result in direct GBM cell destruction or are part of a GBM treatment protocol, e.g., through GBM imaging. I focus on GBM treatments that have been the subject of at least one publication listed in the pubmed search database. I also discuss several scientific, societal, and industrial issues related to early GBM diagnosis, an adapted preclinical model, different methods to yield efficient drug delivery to GBM tumor, program to accelerate the development of GBM therapies, patents protecting various GBM treatments, the different actors tackling GBM, the cost associated with GBM treatment, GBM market figures, and finally a financial analysis of the different companies involved in the development of GBM treatment.

THE DIFFERENT GBM TREATMENTS COMMERCIALIZED OR UNDER DEVELOPMENT

The different drugs and medical devices used for GBM Treatments are summarized in **Figures 1** and **2**. The type of drug, name of company developping it, proposed drug made of section are indicated in **Table 1**. The preclinical/clinical result obtained with these drug are listed in **Table 2**.

Surgery

Surgery is feasible in ∼60% of all GBM patients (Stark et al., 2012). For these patients, it represents the initial treatment and usually consists in maximal safe surgical resection. It leads to the best treatment outcome when the extent of tumor resection is the largest (Stuschke and Thames, 1997; Hess, 1999; Stummer et al., 2008). GBM cells have a tendency to infiltrate normal parenchyma, spread into the ventricles, and to remain in the post-surgical cavity where they can form a new tumor within 2–3 cm of the tumor margin. One major difficulty resides in removing glioma cells remaining within the tumor margin without producing adverse effects such as unintentional damage to surrounding healthy tissues, possibly leading to language and motor deficits. Surgical methods and associated imaging techniques, which are under development to improve the efficacy of surgery and reduce its side effects, are described below.

Methods Used for Maintaining Patients Awake During Surgery

Awake craniatomy (AC) is a method that maintains patient awake during the surgical operation that can be carried out using a neuronavigation system, such as the Stealth Station developed by Medtronic (Parney et al., 2010). Compared with general anesthesia, AC leads to better GBM tumor resection and postoperative functional status, and to reduction in morbidity (Eseonu et al., 2017). Furthermore, AC enables to decrease hospitalization time by 3 days, hence reducing the cost of a surgical operation (Eseonu et al., 2017). However, AC remains relatively complex to achieve, requiring the presence of a multidisciplinary team composed of surgeons, anesthesiologists, and neurologists.

Surgical Robot

Neuroarm, commercialized by Integrated Surgical Systems, is a magnetic resonance imaging (MRI) compatible microsurgery and stereotaxic system that enables the surgeon to see GBM lesions and remove them almost simultaneously. Furthermore, due to its surgical tools that are automatically controlled by measuring the forces that they apply on tumor tissue, Neuroarm can precisely remove part of the GBM tumor (Maddahi et al., 2016). This robot can be useful to reduce surgeon tasks and fatigue (Sutherland et al., 2015), but its use was not yet shown to improve patient survival compared with conventional surgery (Maddahi et al., 2016).

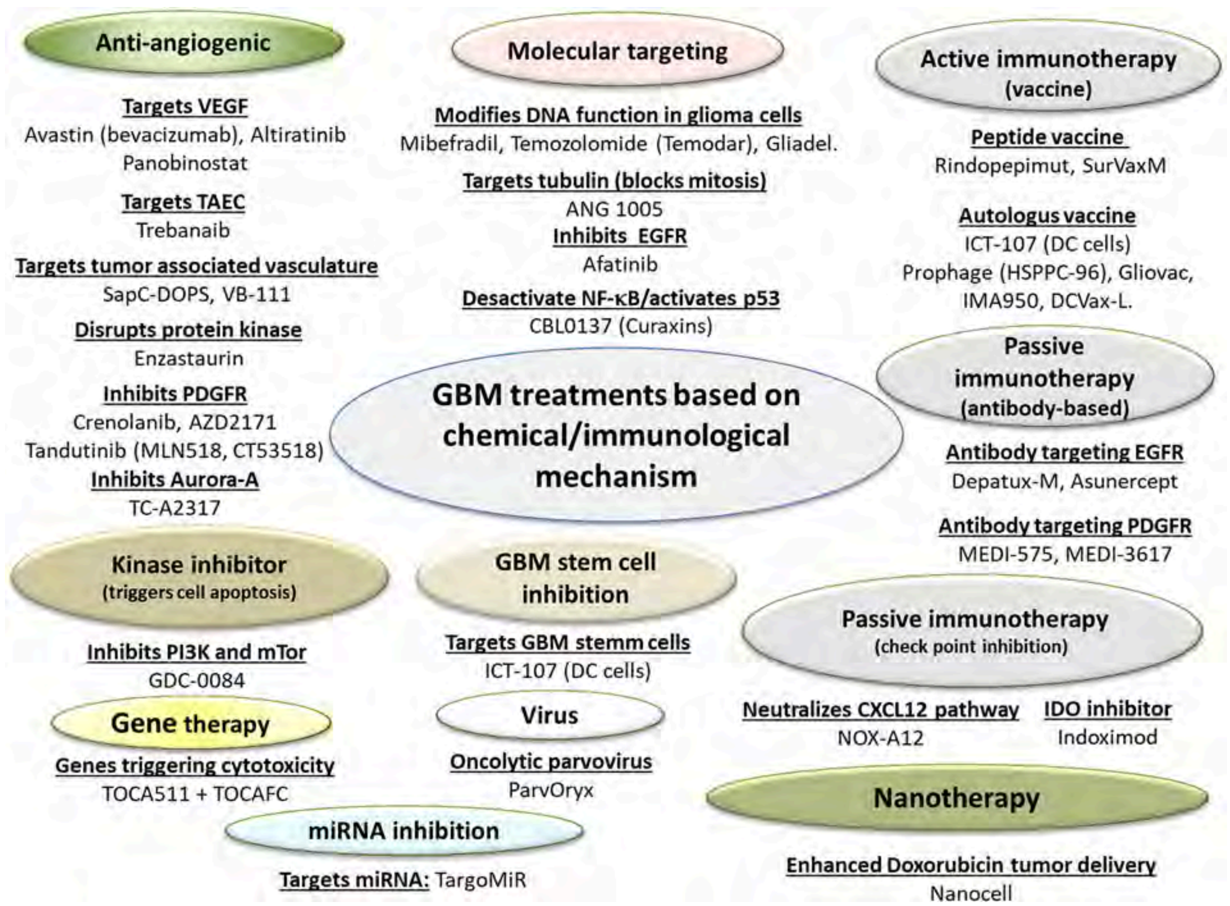

FIGURE 1 | A schematic diagram presenting the different GBM treatments relying on chemical and immunological mechanisms. These treatments are classified as drugs, since their dominant mode of action is immunological, metabolic, or pharmacological. GBM drugs with their associated mode of action are listed.

Imaging Techniques Used During Brain Surgery

Standard imaging techniques such as MRI and computed tomography (CT) can be used to obtain brain maps before a surgical operation. However, since they are not established during the surgical operation, they don't precisely represent brain status or structure during tumor resection, leading to the so-called brain shifts, i.e., discrepancies that have led to numerous side effects such as deformations of cortical and subcortical structures, loss of cerebrospinal fluid (CSF), or brain edema. To improve brain tumor imaging, the following real time techniques have therefore been developed.

Fluorescent imaging systems

Positron emission tomography (PET), using for example Siemens EXACT/HR or ADVANCE NXi positron emission tomograph commercialized by Siemens and GE respectively, is a molecular imaging technique that provides information about molecular processes taking place in GBM tumor. In PET, the nucleus of radioisotopes emits positrons that annihilate when they meet electrons, producing photons that are counted on a detector unit. Different types of radioisotopes are used to monitor specific molecular transformations taking place in GBM, for example Fluoro-2-deoxy-D-glucose ([18F]FDG) for measuring glucose metabolism, radiolabeled amino acids ([11C]methionine), and aromatic amino acid ([18F]fluorotyrosine, [18F]fluoromethyltyrosine, [18F]fluorodopa) to monitor amino acid transport as well as protein synthesis that are enhanced in glioblastoma tumor, Nitroimidazole derivatives ([18F]fluoromisonidazole and [18F]FAZA38) to detect tumor hypoxia, choline analog ([18F]fluorocholine) produced by high grade glioma and their metastases. With the help of this large variety of radiotracers, PET is able to identify malignant regions with a relatively high resolution (1.5 mm at best), and can therefore guide the surgeon during glioma resection (Chiang et al., 2018).

Confocal Laser Endo-microscope (CLEM), for example the Cellvizio system developed by Mauna Kea Technologies, is a fluorescent detection method, which was used during GBM surgery in combination with different contrast agents (5-aminolevulinic acid and fluorescein) and enables to distinguish between healthy and glioma cells (Pavlov et al., 2016).

Optical Coherence Tomography (OCT), which can be carried out with a Sirius 713 Tomograph developed by 4Optics AG, uses near-infrared light penetrating at a depth of up

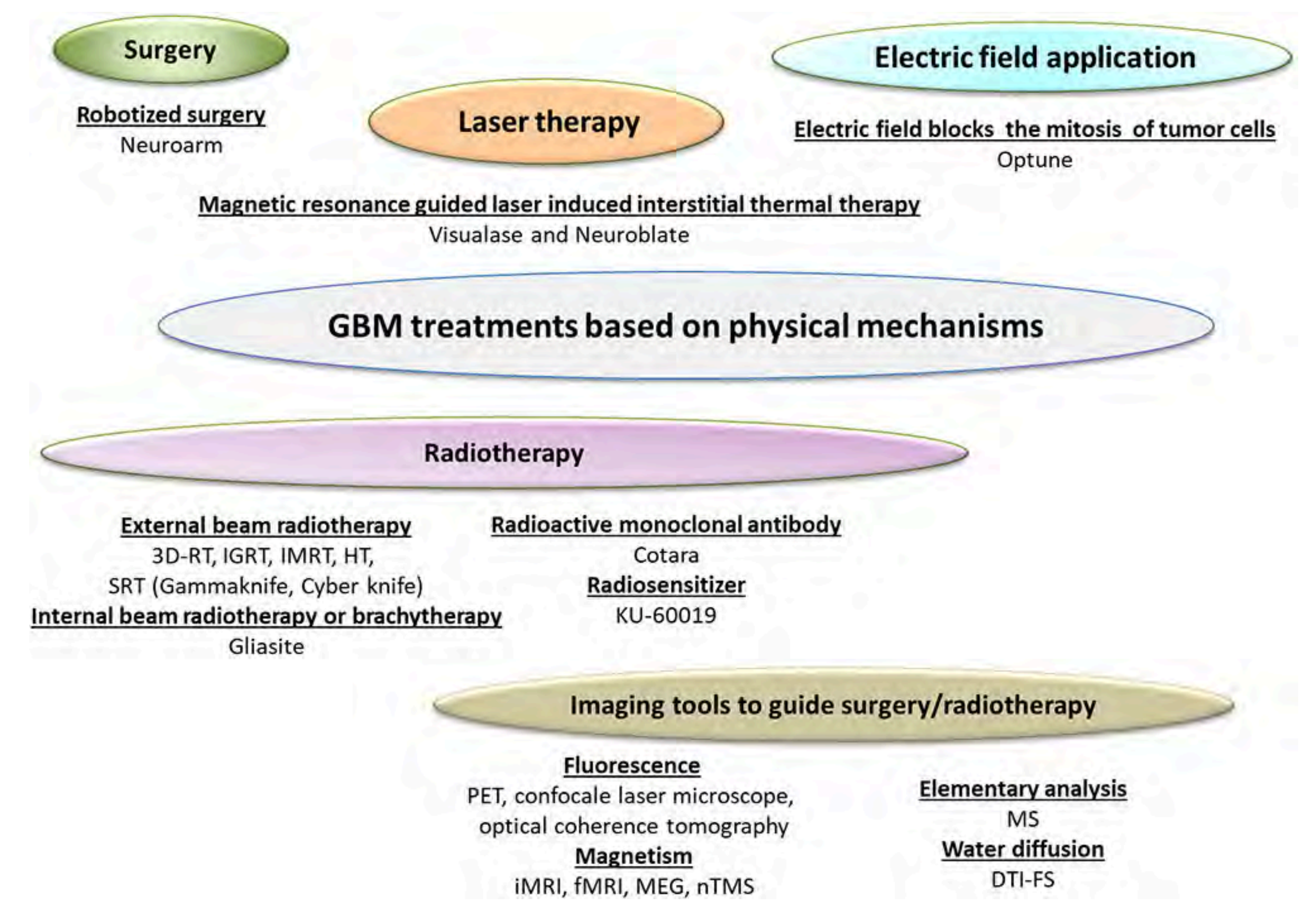

FIGURE 2 | A schematic diagram presenting the different GBM treatments relying on physical mechanisms. These treatments (except Cotara and KU-60019) are classified as medical devices, since their dominant mode of action is not immunological, metabolic, or pharmacological. These GBM treatments with their associated mode of action are listed.

to several millimeters that is reflected to generate cross-sectional images of the brain. Endoscopes could be used to reach glioblastoma tissues during OCT measurements. Different types of OCT endoscopes have been described, integrating side-viewing and forward viewing probes, different scanning mechanism, or being combined with other imaging modalities (Gora et al., 2017). Compared with other imaging techniques, OCT equipment presents the advantages of being relatively cheap while producing images with high axial (1–10 μm) and temporal (10^{-3} s) resolutions without needing any contrast agent. A study has compared OTC images obtained from healthy and GBM human brain tissues extracted from patients. Lower optical attenuation was found in cancer than non-cancer tissues, suggesting that OCT could discriminate between healthy and tumor tissues during a surgical GBM treatment (Kut et al., 2015).

Magnetic imaging systems

Intraoperative magnetic resonance imaging (iMRI) can be divided in two categories. A first type of iMRI developed by IMRIS (IMRISneuro), Philips (Ingenia MR-OR), GE healthcare (MR surgical Suite), Odin Medical Technologies (PoleStar magnet), Medtronic Navigation (PoleStar), is directly conceived to be used as iMRI. A second category of iMRI, commercialized by Hitachi Medical System (AIRIS I and II), Siemens Medical Solutions (Magnetom Open Viva), and BrainLAB (BrainSuite), consists in MRI, which have been modified and adapted to be useable in the operation room (OR). iMRI is used to identify GBM cell location during a surgical operation. It can be subcategorized as iMRI of low field strength (0.12–1.5 T), enabling relatively easy and fast real time imaging but without a high resolution, and iMRI of high field strength (1.5–3 T) that are more difficult to use during surgery due to a longer acquisition time, but provide brain tumor images with enhanced resolution. iMRI has been shown to strengthen the safety of surgical procedure by imaging healthy tissues, hence preventing their removal, to increase the percentage of tumor resection, and possibly rather modest improvement in GBM patient survival (Coburger et al., 2017; Fukui et al., 2017; Khan et al., 2017).

Functional Magnetic Resonance Imaging (fMRI) are commercialized by large companies that already sell standard MRI equipment, such as Siemens (Siemens 3-T Trio fMRI),

TABLE 1 | A list of the different GBM therapies, associated drug names, companies in charge of their development or commercialization, as well as drug proposed mode of action.

Therapy	Drug type	Company name	Proposed modes of action
Afatinib	ErbB family inhibitor	Boehringer Ingelheim	Binds to ErbB receptor and inhibits EGFR activity (glioma cell proliferation).
AFM 21	Bivalently binding TandAb	Affimed therapeutics	TandAbs recruit either cytotoxic T- or NK-cells that eliminate cancer cells with EGFRvIII+.
Aldoxorubicin	Cytotoxic	CytRx	Doxorubicin combined with a linker that binds to circulating albumin. Tumors concentrate albumin, thus increasing the delivery of the linker molecule with the attached doxorubicin to tumor sites. Doxorbucin selectively released at tumor site due to its acidic environment.
Altiratinib	Inhibitor of MET/TIE2/VEGFR2	Deciphera	Prevent or delay bevacizumab-mediated resistance mechanisms.
ANG1005	Paclitaxel-peptide drug conjugate	Angiochem	Paclitaxel modified to cross BBB (Bertrand et al., 2011). It targets tubulin and blocks mitosis.
APG101 (Asunercept)	Antibody conjugated with CD95	Apogenix	Binds and neutralizes CD95L responsible in high motility of glioma cells Merz et al., 2015.
AV0113	Immunotherapy	Activartis Biotech GMBH	Dendritic cell (DC)-based vaccine composed of autologous monocyte-derived DCs exposed to LPS express IL-12 and activate NK cells T-cells against tumor cells.
Avastin (bevacizumab)	Antiangiogenic	Roche	Neutralizing antibody targeting vascular endothelial growth factor (VEGF).
BiCNU	Carmustine	Emcure Pharma Uk Ltd	Dialkylating agent forms interstrand crosslinks in DNA, which prevents DNA replication and DNA transcription.
CBL0137 (curaxins)	Similar to anti-malarial agent	Incuron	Different structure from the tested anti-malarials but similar activation of p53 (tumor suppressor) and suppressing NF-κB (pro-survival transcription factor) without inducing genotoxicity.
Crenolanib	Inhibitor of PDGFRα/β	Arog Pharamceuticals	Inhibtits PDGFR (a type I kinase) that drive glioblastoma growth.
DCVax-L	Vaccine (autologous tumor antigen and patient DC)	Northwest biotherapeutics	Tumor antigens and DC, obtained by surgical resection and leukapheresis, respectively, DCs are mixed and injected back to the patient, allowing DCs to present their surface tumor antigens to the CD4 and CD8 T-cells of the immune system, leading to the activation of T-cells against the tumor.
Depatux-M; ABT-414	EGFR-targeted antibody-drug conjugate	Abbvie	preferentially binds glioma cells with EGFR amplification, is internalized and releases a potent antimicrotubule agent, monomethyl auristatin F (MMAF).
Enzastaurin	Anti-angiogenic	Elly Lilly	Disrupts the protein kinase C (PKC), which is essential for angiogenesis and tumor growth.
Gama Knife	Stereotactic radio-surgery	Elekta	Cobalt-60 machine generating gamma rays over a precise delineated region containing the tumor (tumor size <3 cm).
GDC-0084	Inhibitor of PI3K kinase	Novogen	An inhibitor of phosphoinositide-3-kinase (PI3K) and mTOR, which is able to cross the BBB
Gliadel	Carmustine wafer	Eisai	Wafer containing carmustine implanted into the brain following surgical removal of malignant glioma allows direct delivery of Carmustine to the tumor site.
Gliovac ERC1671	Immunotherapy	ERC	Autologous and allogeneic tumor cells generated from the glioma tumor tissues of three different donor cancer patients, and the lysates of all of these cells. This mixture is injected to stimulate the patient's immune system against the tumor cells.
GMCI (Gene-mediated cytotoxic immunotherapy)	Vaccine-like	Advantagene	Activates adaptive and innate immunity.
ICT-107	Autologous vaccine	Immunocellular	Targets tumor antigens highly expressed on glioblastoma cancer stem cells.
IMA950	Vaccine	Immatics Biotechnologies	11 different HLA-restricted tumor-associated peptides over-expressed on the surface of glioblastoma tumors trigger the immune system to recognize and kill tumor cells while leaving healthy cells unharmed.
Indoximod	IDO inhibitor	Newlinkgenetics	Inhibits IDO (indoleamine 2,3-dioxygenase) that inactivates NK (natural killer) cells and generates Tregs (regulatory T cells).
KML001	A telomere targeting drug	Komipharm International	Sensitizes glioblastoma cells to temozolomide chemotherapy and radiotherapy through DNA damage and apoptosis.
MEDI-575	human IgG2 Antibody	MedImmune	High affinity and specificity for human PDGFRα, reducing the growth of GBM tumors.

(Continued)

TABLE 1 | Continued

Therapy	Drug type	Company name	Proposed modes of action
Mibefradil	Cytotoxic	Cavion	Inhibits Cav3 (T-type calcium channel essential for external calcium entry in glioma cells), hampers a glioma cell ability to repair double-strand DNA breaks and causes cancer cell cycle arrest and apoptosis.
Nanocell	cytotoxic	EnGeneIC	Nanocellulars (minicell) contain Doxorubicin and target EGFR overexpressed in tumors via minicell-surface attached bispecific proteins (Vectibix).
Neuroblate	MRgLITT	Monteris	Both diffusing (FullFire) and side-firing (SideFire) directional laser delivery probes (LDPs). Pulsed laser of 1,064 nm with maximum power of 12 W also including a controlled cooling mechanism. Temperature monitored by real-time MR thermography (Lagman et al., 2017).
NOX-A12	Neutralizes CXCL12	Noxxon	Neutralizes chemokine CXCL12 pathway, which promotes cancer cell survival, facilitates tumor recurrence and metastasis, and promoting angiogenesis. NOX-A12 also fights tumors by: (i) breaking tumor protection against immune cells T-cells, (ii) blocking tumor repair, (iii) exposing hidden tumor cells.
Optune	Tumor-treating fields	Novocure	Generates an alternating current (100–300 kHz) that alters tumor cell polarity and blocks tumor cell mitosis.
ParvOryx	Virus	Oryx	Oncolytic parvovirus H1 (H-1PV) that infects and lyses GBM tumor cells. Due to its small size, it crosses the BBB. It does not affect normal cells and is not pathogenic to humans. I allows for both intratumor and intravenous administration as well as repeated application.
Prophage (G100 and G200)	Vaccine (patient specific)	Agenusbio	Use of the heat shock protein gp96 (HSPPC-96), purified from tumor tissue inducing immune response against the tumor.
PSMA ADC	Antiangiogenic	Ambrx	PSMA-targeted monoclonal antibody conjugated with microtubule disrupting agent monomethyl auristatin E (MMAE) targets PSMA, transmembrane peptidase upregulated on endothelial GBM cells.
Rindopepimut (CDX-110)	Peptide vaccine	Celldex	Anti-EGFRvIII immune responses. EGFRvIII (most common in primary glioblastoma tumors) is a tumor-specific epitope expressed on ∼20–30% of GBMs, containing a tyrosine kinase that has pro-oncogenic effects.
SapC-DOPS	Anti-angiogenic.	Bexion pharmaceuticals	Affinity for phosphatidylserine in the outer membrane of tumor-associated vasculature of GBM.
Selinexor (KPT-330)	Small molecule	Karyopharm Therapeutics	Selinexor inhibits nuclear export protein XPO1 that inactivates tumor suppressor protein.
TC-A2317	Aurora-A inhibitor	Takeda	Inhibits Aurora-A, a serine/threonine kinase that drives GBM cell cycle progression.
Temodar (Temozolomide)	alkylating agent	Merck	Breaks DNA double-strand, causing cell cycle arrest and cell death.
Toca 511 + Toca FC	Gene therapy + prodrug	Tocagen	Toca 511 encodes and delivers cytosine deaminase (CD) gene to tumor. Toca FC induces transformation of 5-fluorocytosine in 5-fluorouracil in tumor cells having expressed CD gene.
Trebanaib AMG 386	Antiangiogenic	Amgen	Peptide-Fc fusion protein that blocks angiopoietin-Tie2 signaling and inhibits proliferation of Tumor Associated Endothelial Cells.
VAL-083	chemotherapy	DelMar Pharmaceuticals	Cytotoxicity (claimed to be larger than for TMZ), can overcome resistance associated with MGMT (O6-DNA methylguanine methyl-transferase), a DNA repair enzyme that causes resistance to TMZ.
VB-111	Immunotherapy	VBLRX	Combination of tumor vasculature blockade with anti-tumor immune response.
Visualse	MRgLITT	Medtronic	Laser at 980 nm with maximum power of 15 W used to heat and destroy tissue during neurosurgery. Probe tip cooled down by saline circulation. Temperature monitored by real-time MR thermography, (Lagman et al., 2017).

Philipps (Achieva 3.0T X-series scanner combined with the Eloquence system), GE Healthcare (BrainWave). fMRI enables to acquire blood oxygen level dependent (BOLD) MRI scans of the brain and hence to detect metabolic changes and abnormalities that are induced by changes in brain oxygen concentration. It complements standard MRI imaging, which only provides morphological information of the cerebral cortex. fMRI is used during brain surgery to detect parts of the brain that need to be kept in place such as those responsible for the production of speech or comprehension, which cannot be seen with standard MRI (Salama et al., 2018).

Magnetoencephalography (MEG) equipment, which is commercialized by companies such as Elekta (Elekta Neuromag

TABLE 2 | A list of the different GBM drugs, with a summary of the publically available preclinical and/or clinical results.

Drug name	Preclinical/Clinical/results
Afatinib	Manageable safety profile but limited activity (Reardon et al., 2014b).
AFM21	N.A.
Aldoxorubicin	Tumor growth delay observed in mice bearing U87-Luc tumors after injection of Aldoxorubicin (Marrero et al., 2014).
Altiratinib	Tumor growth delay observed in mice bearing GSC11 and GSC17 glioblastoma (Piao et al., 2016).
ANG1005	Mice bearing U87 MG glioblastoma treated with ANG1005 display enhanced tumor growth delay compared with those treated with free paclitaxel (regina2008).
APG101 (Asunercept)	Phase II on 9 patients with recurrent glioblastoma: PFS at 6 months were 20.7% for RT + APG101 compared with 3.8% for RT alone. Improved survival warrants further studies for confiration (Wick et al., 2014).
AV0113	N.A.
Avastin (bevacizumab)	Partial antitumor activity in mice with sarcoma tumors (Presta et al., 1997). Phases II and III: No improvement in survival when Avastin is used as first and second-line therapy, and both in association with cytotoxic treatment or alone (Lombardi et al., 2017).
BiCNU	N.A.
CBL0137	IV injection of CBL0137 ± TMZ in mice bearing U87MG/A107 GBM Increases mouse maximum survival by 10–60 days.
Crenolanib	Glioma cell inhibition.
DCVax-L	Phase II suggests efficacy with 33% of patients reaching or exceeding median survival of 48 months and 27% reaching or exceeding median survival of 72 months. Two patients reached a survival of more than 10 years (Polyzoidis and Ashkan, 2014). Phase III on 331 patients on going.
Depatux-M; ABT-414	Clinical trial on 66 patients leads to PFS at 6 months of 28.8%.
Enzastaurin	Phase III: 266 patients with recurrent glioblastoma treated. Enzastaurin well tolerated and better hematologic toxicity profile than lomustine but no superior efficacy compared with lomustine (Wick et al., 2010).
ERC-1671	One patient receiving ERC-1671 survived for 10 months after the vaccine administration without any other adjuvant therapy and died of complications due his previous therapies (Bota et al., 2015). For 9 patients treated with ERC-1671, 6-month (26 weeks) survival for the nine Gliovac patients was 100 vs. 33% in control group (Schijns et al., 2015).
Gama Knife	Clinical results are too preliminary. Survival benefit still needs to be demonstrated in a phase III clinical study (Elaimy et al., 2013).
GDC-0084	Mice bearing U87 MG glioblastoma injected with GDC-0084 exhibited tumor growth delay (Heffron et al., 2016).
Gliadel	3 clinical trials with increased survival by 6–13 months. 3 clinical trials without increased survival, (Zhang et al., 2013). MA: 1998.
GMCI	80% of mice bearing GL-261 tumors treated with PD-1 and GMCI cured (Speranza et al., 2018).
ICT-107	Phase I: prolonged overall survival and PFS (preliminary data, Phupahnich et al., 2013).
IMA950	Clinical Trial: 49 patients with GBM treated with IMA950. PFS was 74% at 6 months and 31% at 9 months.
Indoximod	Tumor growth delay observed in mice bearing GL-261 glioblastoma tumors injected with Indoximod (Hanihara et al., 2016).
KML001	Clonogenic survival of GBM cells was significantly decreased by the combination of KML001 and TMZ or irradiation (Woo et al., 2014).
MEDI-575	Phase II on 56 patients receiving MEDI-575 showed that MEDI-575 was well tolerated but had limited clinical activity (Phupahnich et al., 2013).
MgLITT (Neuroblate Visualase)	Treatment relatively well tolerated. Minimal BBB permeation (Carpentier et al., 2012). In 16 patients with GBM, Improved survival by 2 months (survival benefit warrants further study) (Schwarzmaier et al., 2006).
Mibefradil	Well tolerated and activity on some patients (Holdhoff et al., 2017).
Nanocell	First in man shows that nanocell was well tolerated in patients bearing glioblastoma (Whittle et al., 2015).
NOX-A12	Mice bearing G12 GBM tumors injected with B-20 and NOX-12 led to an increase in maximum survival by 15 days.
Optune	Increase in time to disease progression from 13 to 26 weeks and of PFS6 from 15 to 50% and OS from 6 to 14.7 months (Saria and Kesari, 2016).
Panobinostat	Phase II on 15 patients, Panobinostat well tolerated, but no significant improvement in PFS6 compared with SOC (Lee et al., 2015).
Parvovirus	In a phase I study, parvovirus was well tolerated and immune response was observed (Geletneky et al., 2017).
Prophage	Phase II: Prophage + radiation and temozolomide lead to: (i) a 146% increase of PFS (17 months compared with 6.9 months for SOC), (ii) a 60% increase of OS (23.3 months compared with 14.6 months for SOC), (Chakraborty et al., 2016).
PSMA ADC	Phase II on 6 patients (trial NCT01856933), efficacy not observed (Elinzano et al., 2016).
Rindopepimut (CDX-110)	Phase II: demonstrating significantly increase by 10 months in PFS, minimal adverse effects (Babu and Adamson, 2012). Phase III (trial NCT01480479) did not confirm increases in PFS observed during phase II (Desaia et al., 2016; Gerstner, 2017; Weller et al., 2017).

(Continued)

TABLE 2 | Continued

Drug name	Preclinical/Clinical/results
SapC-DOPS	Tumor growth delay in mice bearing U87 (Wojton et al., 2013; Blanco et al., 2014, 2015).
Selenexor	Mice bearing patient derived GBM genograft model inhibit tumor growth delay following Selenexor injection (Green et al., 2014).
SurVaxM	Among 9 patients treated, 7 survived more than 12 months. Requires more clinical data to conclude about treatment efficacy (Fenstermaker et al., 2016).
Tandutinib	Phase II was closed due to a lack of efficacy (Batchelor et al., 2016).
TC-A2317	GB neurosphere cells treated with alisertib for short periods undergo apoptosis (Van Brocklyn et al., 2014).
Temodar (Temozolomide)	Radiotherapy + Temozolomide: 2 months increase in overall survival, 15% increase in the percentage of patients alive after 2 years (Lee, 2017). Efficacy of TMZ limited due to MGMT that repairs DNA in tumor cells and reduces the effect of this alkylating agent and overexpression of EGFR. MA:2009.
Toca 511 + FC	High percentage of mice (40–100% depending on injected dose) bearing U87, Tu-2449 glioblastoma are alive 3–10 months following tumor cell implantation (Hiraoka et al., 2017).
Trebanaib AMG 386	Phase II on 48 patients, treatment well tolerated but no improvement in survival (Reardon et al., 2018).
VAL-083	Clinical trial (NCT02717962) ongoing.
VB-111	Tumor growth delay in mice bearing U87-MG injected with VB-111 (Gruslova et al., 2015).

M.A, Market Authorization; NA, Not Available.

TRIUX), is a functional neuroimaging technique that maps brain activity by recording magnetic fields produced by electrical currents occurring naturally in the brain. Since the strength of these magnetic fields is very low (~10^9 lower than the earth magnetic field), it uses very sensitive magnetometers (SQUID sensors) to record them. MEG can be used during GBM surgery to identify locations of brain abnormalities using direct measurements of neuronal activity without necessitating full patient immobilization. However, the main drawback of this technique comes from the high cost of the MEG equipment, which does not seem to be widely used for GBM treatment (Szymanski et al., 2001).

Navigated transcranial magnetic stimulation (nTMS), commercialized by companies such as Magstim (Rapid) or Nexstim (eXimia), delivers magnetic stimulation to spots on the motor cortex. The resulting electrical activity is monitored by electromyography (EMG). nTMS enables to obtain a map of the motor cortex area and hence to optimize tumor resection by preventing removal or damage of eloquent motor areas. It was also shown that the use of nTMS in GBM patients increases the rate of gross total resections by 17% (Frey et al., 2014).

Other imaging systems

Diffusion tensor imaging fiber tracking (DTI-FT), developed by Brainlab (iPlanCranial), slicer (Slicer4), and Medical Analysis and Visualization (MedAlyVis), is a noninvasive imaging technique that measures the diffusion of water molecules in three dimensions within tissue through the application of multiple diffusion gradients. More specifically, it enables visualization of white matter tracts (WMT) often localized near glioma cells (Hana et al., 2014; Mickevicius et al., 2015).

Intraoperative mass spectrometry (MS), uses an equipment such as Desi 2D developed by Prosolia, which is integrated in the operation room and delineate tumor regions by identifying and characterizing the mass and fragmentation patterns of the molecules involved in GBM at the nanometer scale (Pacholski and Winograd, 1999; Stoeckli et al., 2001; Agar et al., 2011).

Treatments Based on the Application of an External Source of Energy

Apart from the radio-sensitizer KU-60019 that has only been tested on mice, GBM treatments using an external source of energy have been tested on humans.

Radiotherapy

In current radiotherapy treatments of GBM, patients are usually exposed to fractionated localized radiation using a standard dose of radiation of 60 Gy, delivered in 30–33 fractions of 1.8–2 Gy (Fuller et al., 2007). Radiotherapy treatments can be carried out using external or internal radiation sources, radioactive monoclonal antibodies, possibly using radio-sensitizer to enhance the effects of radiations.

External beam radiation therapy (EBRT)

EBRT is the most frequently method, which is used for administering radiation therapy (X-ray and protons essentially) to glioblastoma tumors. High energy rays or beams produced outside of the brain are orientated toward the tumor to cover the whole tumor volume (Mann et al., 2018).

Three dimensional conformational radiation therapy (3D-RT) or Image guided radiation therapy (IGRT) use Clinac, Radixact, or Synergy equipment, commercialized by Varian, Accuracy, and Elekta, respectively, that generate X-ray photons

of typically 4–20 MV. In this treatment, the glioblastoma tumor is first imaged in 3D using CT, MRI, PET, or PET-CT scan, and a computer program then designs the orientation of the radiation beam applied on patient's head to cover the whole tumor volume while sparing healthy tissues. Patients are typically exposed to 50–90 Gy (Tanaka et al., 2005; MacDonald et al., 2007; Thibouw et al., 2017). In a clinical trial involving 184 GBM patients, survival at 5 years was shown to reach 51 and 15% following 3D-RT and non-conventional radiotherapy, respectively (Tanaka et al., 2005), indicating that 3D-RT increases patient's survival compared with non-conformational radiation therapy.

Intensity modulated radiation therapy (IMRT) uses Radixact (Accuracy), Infinity or Precise treatment system (Electa), Vitalbeam or Clinac (Varian). It is similar to 3D-RT or IGRT, but has the additional feature of allowing an adjustment of the strength of the radiation beam, depending on the targeted region of the glioblastoma tumor. Compared with 3D-RT or IGRT, IMRT enables to deliver higher radiation doses within a shorter period of time without any toxicity increase (Amelio et al., 2010; Burnet et al., 2014). Treatment typically involves daily sessions of 10–20 min during 6–8 weeks.

Helical-tomography (HT) uses a HT system, commercialized by Accuray for example. HT is a type of IMRT that uses computed tomography (CT) to guide the X-ray beam to the desired tumor location. HT produces a narrower beam than LINAC used in conventional IMRT. This beam is delivered while the patient is moving enabling to better target different tumor sites without the need for a pause between different patient positions. HT was reported to better spare organ at risks than LINAC during GBM radiation therapy (Miwa et al., 2008; Koca et al., 2014).

Stereotactic radiosurgery (SRT), carried out by Apex or Versa HD (Elekta), Truebeam or ClinaciX system (Varian), Artiste solution, Oncor K or M Class, Primus (Siemens Healthineers), is a non-invasive treatment method that uses pencil-thin beams of X-ray radiation that are focused on GBM tumor. Patient's head may be inserted in a frame, an imaging technique such as CT or MRI is used to locate the tumor and deliver the energy at tumor location. Compared with IMRT, SRS presents the advantage of delivering X-ray energy within less sessions (<5) during 6–8 weeks, using higher doses of radiation during each session (Yanagihara et al., 2016).

Gamma knife, commercialized by Elekta for example, is a specific type of SRT. It delivers a large number of X-ray beams (>200) that are focused on the GBM tumor with the help of a computer. Gamma knife was reported to be a safe treatment option for patients diagnosed with recurrent GBM. In terms of efficacy, it yielded a median survival after tumor recurrence ranging from 13 to 26 months, which is not significantly better than with other types of radiotherapies. When it was combined with chemotherapy, improved survival may have been observed among GBM patients, but a phase III appears necessary to confirm this result (Elaimy et al., 2013).

Cyber knife, commercialized by Accuray for example, is another specific type of SRT. Compared with Gamma Knife, Cyber knife presents the advantages of not requiring a metal frame around patient's head, of letting the patient lie while the radiation system moves around its head, and of not needing the patient to be anesthetized. Although Cyber knife presents several interesting technological features, it actually seems to have led to GBM tumor appearance when it was used to treat a patient with brain arteriovenous malformation (Xhumari et al., 2015). The balance between anti and pro tumorigenic effects of Cyber knife and other radiotherapy equipment should therefore be carefully examined before starting the treatment.

Proton radiation therapy (PRT) is carried out with an equipment such as Radiance 330 commercialized by Pro Tom International that generates proton beams, which deliver energy of 70–250 MeV within the tumor location. Compared with X-rays, PRT induces less energy penetration in healthy tissues than X-rays. It enables to reach antitumor efficacy using a lower level of radiation than X-rays and to minimize the exposure of radiations to organs at risks such as the hippocampi, sub-ventricular zones, hearing and visual apparatus, and pituitary gland. Several clinical trials, carried out on GBM patients treated by proton therapy, reported that this therapy was well tolerated, but they did not firmly conclude in an improvement in patient survival, due to the too small number of treated patients (Galle et al., 2015; Adeberg et al., 2017). Proton therapy may be of specific interest in children, which are more affected by long-term effects of x-ray therapy than adults.

Internal radiation therapy (IRT) or brachytherapy (BT)

Brachytherapy uses a radioactive substance located near or in the GBM tumor to deliver radiation therapy (Barbarite et al., 2017). BT enables to reduce side effects including damages to healthy tissues by concentrating the radiation beam in the regions where the tumor is located or is most the likely to recur. The longest median overall survival following BT that have been reported so far are 28 and 16 months for patients with newly diagnosed and recurrent GBM, respectively. Initially, a radioactive material was directly inserted in the GBM tumor. To avoid that physicians are exposed to a too large quantity of radiations, the radioactive material can be inserted in a catheter connected to the tumor. BT can be divided between low-dose rate brachytherapy (LDR-BT) and high-dose rate brachytherapy (HDR-BT), delivering less or more than 30 cGy/h, respectively. LDR-BT leads to less side effects than HDR-BT and to better benefit/risk ratio, but takes a longer time and induces more patient discomfort than HDR-BT. The radioactive substance used in BT is usually either I-125 (Iodine-125) or 192-Ir (iridium 192).

Gliasite, initially developed by Hologic and currently commercialized by Isoray, consists of a balloon, which is positioned in or near the GBM tumor during surgery and is then filled with a radioactive material containing I-125 (Iotrex [sodium 3-(^{125}I)-iodo-4-hydroxybenzenesulfonate]). Gliasite enables the delivery of radiation dose to areas that are most at risk of recurrence. A clinical study carried out on 24

patients suffering from recurrent GBM showed that the treatment was safe, but it did not conclude in improved patient survival compared with other types of radiotherapies (Chan et al., 2005).

Radioactive monoclonal antibodies

Cotara, developed by Peregrine Pharmaceuticals, is a ^{131}I-labeled chimeric monoclonal antibody that was designed to diffuse to necrotic area of GBM tumor and to bind to specific antigens expressed in cells belonging to this part of the tumor (histone H1 complexed with deoxyribonucleic acid). Cotara should then deliver a cytotoxic dose of ^{131}I radiation to the adjacent living GBM cells (Patel et al., 2005). Clinical trials (phase I, NCT00509301 and phase II, NCT00677716) were carried out leading to a 2 months improvement in survival among 40 GBM patients in 2011. However, this result was not confirmed in a phase III and the author is unaware of any further clinical developments using radioactive monoclonal antibody for GBM treatment since 2011.

Radiosensisitizer

Several molecules were reported to increase antitumor efficacy of radiation when they were present in the tumor during radiation.

KU-60019, under development by AstraZeneca, is a kinase inhibitor, which was shown to radiosensitize glioma cells both *in vitro* (Golding et al., 2012) and *in vivo* on mice bearing GBM tumors (Vecchio et al., 2014). In mice bearing GBM, treatment consisting in KU-60019 administration and radiation led to a 25 days increase in survival compared with radiation alone (Vecchio et al., 2014).

Electric Field Therapy

Tumor treating fields (TTFields), commercialized by Novocure, uses Optune consisting in electrodes positioned on patient's head that generate low intensity electric fields alternating at a frequency of 200 kHz, which selectively block tumor cell division during mitosis by interrupting during metaphase and/or anaphase the spindle assembly unusually occurring in healthy cells (Mun et al., 2017). When U-118 glioma cells were treated with TTF combined with standard chemotherapeutic drugs (Paclitaxel, Doxorubicin, Cyclophosphamide), it resulted in the destruction of most living cells after 70 h of treatment, while the drugs or TTF alone only slowed down cancer cell proliferation, suggesting that TTF should be combined with another treatment modality to reach optimal efficacy (Kirson et al., 2008), Preclinically, rats bearing intracranial GBM were treated with TTF during 6 days, leading to smaller tumors for treated than untreated rats. Interestingly, this study underlines the necessity of applying TTF in several directions to yield antitumor efficacy (Kirson et al., 2007). The author is not aware of a study showing full disappearance of GBM tumors in mice/rats treated with TTF and it seems that this treatment went directly to clinical trials without such demonstration. The efficacy of TTF was assessed clinically on patients with recurrent or newly diagnosed GBM (Benson, 2018). In particular, in a phase III clinical study involving 466 patients (EF-11), the addition of TTFields to standard therapy was shown to increase median overall survival from 15.6 without TTF to 20.5 months with TTF, to improve patient quality of life, and to lower incidence of serious adverse events (Stupp et al., 2015). Optune seems to be one of the only recent treatments leading to a statistically significant improvement in survival for patients suffering from GBM. However, such improvement is relatively modest and implies a very large increase in treatment cost by an average of 185,476 euros per patient (Bernard-Arnoux et al., 2016).

Laser Therapy

Magnetic resonance guided laser-induced interstitial thermal therapy (MRgLITT) has been developed by Monteris (Neuroblate and Visualase). In this treatment, Magnetic Resonance Imaging is first used to localize the GBM tumor, a laser beam is transmitted through fiberoptics toward the tumor region and the resulting thermal energy heats the tumor at an average temperature of 43°C. Thermography enables to monitor and adjust temperature changes during the treatment. The mechanisms by which heat induces tumor destruction remain poorly understood, but possibly involve protein denaturation, membrane dissolution, vessel sclerosis, and coagulative necrosis. MRgLITT can serve to destroy tumor parts located in regions of the brain that are difficult to access and would possibly lead to injury of adjacent functional structures if surgery was used. Visualase and Neuroblate systems operate at relatively similar wavelengths of 980 nm and 1,064 nm, respectively, and powers of 12–15 W. However, the Neuroblate system can more precisely adjust light diffusion in the tumor by using both diffusing and side scattering modes compared with Visualase that only operates with a diffusing mode (Lagman et al., 2017). Furthermore, the Visualase system has only rarely been used for GBM treatment, its main therapeutic target being epilepsy (Patel et al., 2016). A first clinical trial carried out on 10 patients with 15–40 mm GBM tumor resulted in tumor necrosis 24–48 h following Neuroblate treatment (NCT007472253) (Sloan et al., 2013). Another clinical trial on 34 GBM patients did not show any improvement in survival for patients treated with Neuroblate, but it underlined the importance of heat homogenous distribution to reach the best treatment outcome (Mohammadi et al., 2014). It was also shown on 20 patients suffering from GBM that the Neuroblate system could open the BBB between 1–2 and 4–6 weeks following MRgLITT treatment, and hence possibly favor the diffusion of drugs through the BBB during this lapse of time (NCT01851733) (Leuthardt et al., 2016).

Radiofrequency Treatment (Non-thermal and Thermal)

Radiofrequency hyperthermia was carried out on GBM patients by inserting electrodes into GBM tumors using CT-guided stereotaxis and applying 13 MHz radiofrequency hyperthermia during 1 h, leading to: (i) an increase in tumor temperature that remained below 43°C, (ii) the destruction of the BBB enabling chemotherapeutic drugs to reach the tumor, (iii) an absence of side effects. The treatment led to 80% of necrotic tumor and to a decrease in tumor diameter. Further assessment of this treatment is however necessary to conclude about its efficacy on a larger number of patients (Sun et al., 2013).

A device generating ultralow radiofrequency without inducing heat (Nativis Voyager) was developed by the company Nativis. It is supposed to enhance tubulin polymerization and inhibit cell division (Butters et al., 2014). In a first clinical trial involving 14 patients suffering from GBM (NCT02296580), treatment with Nativis Voyager was reported to result in no serious adverse events and in a progression free disease among 2 patients (Barkhoudarian and Wayne, 2017).

Hyperthermia Therapy With Ultrasound

An ultrasound device approved by the FDA and commercialized by Insightec (Exablate Neuro) focuses ultrasound waves to GBM to heat and ablate these tumors. A first in man study carried out on a patient suffering from recurrent GBM demonstrated that high-power sonications could be applied on GBM with the help of MRI, yielding partial tumor ablation without adverse effects (Coluccia et al., 2014).

Molecular Targeting

Drugs Targeting GBM at Molecular Levels Used on Humans

Mibefradil, under development by Cavion, is a drug that selectively blocks T-type channels, which are overexpressed in GBM tumors and are involved in angiogenesis and invasion of tumor cells. In a phase II study, Mibefradil was administered to 27 GBM patients. It was well tolerated and resulted in some responses, i.e., it increased overall survival (OS) and progression free survival (PFS) of GBM patients by 15 and 2 months, respectively (Holdhoff et al., 2017). However, efficacy needs to be confirmed on a larger cohort of patients.

Temozolomide (TMZ), which is commercialized by Merck, is an alkylating agent that breaks DNA double-strand and also reduces the activity of a DNA repair enzyme, called O 6 methylguanine-DNA methyltransferase (MGMT), hence promoting GBM tumor cell death (Thomas et al., 2017). It is one of the only chemotherapeutic drugs, which has shown some clinical efficacy and is currently prescribed to treat GBM. It is used following radiotherapy treatment at a daily dose of 150–200 mg/m^2 of body-surface area (BSA) for 5 days every 28-day cycle. In a large phase 3 clinical trial, the efficacy of a treatment using TMZ with concomitant radiation therapy followed by adjuvant TMZ for 6 months was shown to improve median overall survival (MOS) and 2-year survival by ~2 months and 16%, respectively compared with a treatment using only radiation (Stupp et al., 2005).

Gliadel, which is sold by MGI Pharma, is composed of wafers containing biodegradable polymers containing 3.85% carmustine that are placed in the resection cavity at the time of surgery for patients with primary or recurrent GBM. Carmustine is an alkylating agent of DNA and RNA. It has been shown to improve median survival of GBM patients by 2–4 months (Chaichana et al., 2011), and resulted in adverse effects that were significant but not superior to those observed with SOC (Perry et al., 2007).

Val-083 (Dianhydrogalactitol), under development by Del Mar Pharmaceuticals, was reported to cross the BBB, to be absorbed more importantly in cancer than healthy cells, to bind to GBM cell DNA, leading to GBM cell death with more efficacy than other DNA drugs. VAL-083 was shown to be active against MGMT-unmethylated GBM cells which are resistant to treatment with TMZ and nitrosoureas. In a clinical trial, it increased GBM patient OS by 8 months (Eagan et al., 1979). For some reasons unknown to the author, despite of promising clinical efficacy, VAL-083 (dianhydrogalactitol) was not widely used since 1979 and seems to have been re-discovered only recently.

Afatinib, which is under development by Boehringer Ingelheim, is an irreversible inhibitor of epidermal growth factor receptor (EGFR), tyrosine kinase activity, and tumor cell proliferation (Taylor et al., 2012). In a phase I/II study, Afatinib was shown to have a manageable safety profile but resulted in limited activity among patients with recurrent GBM (Reardon et al., 2014a).

Drugs Targeting GBM at Molecular Levels Tested Pre-clinically

Aldoxorubicin, developed by CytRx, contains doxorubicin, a well-known intercalating DNA agent, combined with a linker-molecule that specifically binds to albumin in the blood. Compared with Doxorubicin, Aldoxorubicin increases the amount of drug delivered while minimizing toxicity. When immune compromised mice bearing GBM tumors were treated with aldoxorubicin, the drug was observed to accumulate in the tumor and not in normal brain, to reduce the number of GBM dividing cells, and to lead to an OS of more than 63 days, compared with ~25 days for animals treated with doxorubicin or saline (Marrero et al., 2014).

ANG-1005, which is under development by Angiochem, consists of three molecules of paclitaxel conjugated to a peptide acting as a brain delivery vector (Angiopep-2), which improves penetration through the BBB by transcytosis (Bertrand et al., 2011). Once inside glioma tumors, paclitaxel is expected to prevent microtubule de-polymerization, and hence to inhibit tumor cell proliferation. Mice bearing U87 MG glioblastoma, which received ANG1005 at a dose of 50 mg/kg, were shown to live 3 days longer than untreated mice (Régina et al., 2008).

CBL0137 (Curaxin), which is under development by Buffalo Biolabs and Incuron, is expected to trigger antitumor activity by binding to DNA and inactivating the Facilates Chromatin Transcription (FACT) complex, which repairs transcription and replication mechanisms of DNA. In mice bearing U87 GBM, the administration of 35–70 mg/kg of CBL037 and TMZ was shown to increase mouse maximal survival by 55 days compared with untreated mice (Barone et al., 2017).

Anti-angiogenic

Anti-angiogenic GBM Drugs Used on Humans

Bevacizumab (BV, avastin), which is commercialized by Genentech for GBM treatment, is a human monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), and has been approved for GBM treatment since 2009 in the USA. However, for patients suffering from GBM, the use of BV does not increase survival by more than 4 months in average and other benefits in terms of improved quality of life have not been

demonstrated (Diaz et al., 2017). Studies combining the use of BV with other cytotoxic drugs have been published (Herlinger et al., 2016) or are currently ongoing to examine potential additional patient survival benefit with these combinations (Tamura et al., 2017).

MLN518 (Tandutinib), which is under development by Millennium Pharmaceuticals, is an inhibitor of type III receptor tyrosine kinase (PDGF receptor-β, Fms-like tyrosine kinase 3, c-Kit). A first phase II study carried on patients receiving MLN518 with recurrent GBM was closed due to the lack of efficacy of the treatment (Batchelor et al., 2016). Another phase II clinical study investing the combination of BV with MLN518 for GBM treatment reported enhanced toxicity without improved efficacy compared with BV alone (Odia et al., 2016).

Enzastaurin, which is developed by Eli Lilly, is expected to specifically target and inhibit protein kinase C (PKC), hence preventing tumor growth and proliferation. Two phase II studies, which enrolled between 66 and 88 patients, did not show increased survival in patients receiving Enzastaurin compared with untreated patients (Kreisl et al., 2010; Butowski et al., 2011). In another phase II study on 81 GBM patients, Enzastaurin treatment combined with BV did not improve patient survival compared with treatment using BV alone (Odia et al., 2016). A phase III study carried out on 266 patients, which compared Enzastaurin and laumustine treatments, did not conclude in improved efficacy using Enzastaurin (Wick et al., 2010).

AZD2171 (Cediranib), under development by AstraZeneca, is an anti-angiogenic drug that inhibits tyrosine kinase with activity against PDGF receptors and c-Kit. Preclinical studies carried out on mice bearing U87, U118, and CNS1 glioblastoma, which received Cediranib orally, showed that this drug did not affect tumor growth, but led to a slight increase in mouse survival by 5–10 days compared with untreated mice (Kamoun et al., 2009). In a phase III clinical study on 325 GBM patients, who were first treated by radiotherapy and TMZ chemotherapy, administration of AZD2171 alone or on combination with lomustine did not result in PFS improvement (Batchelor et al., 2013). A phase I study, in which GBM patients were treated with Cediranib and Cilengitide, also concluded in the absence of treatment efficacy (Gerstner et al., 2015).

Anti-angiogenic GBM Drugs Tested on Animals

Altiratinib (DCC-2701), which is under development by Deciphera Pharmaceuticals, is an anti VEGF drug that was designed to overcome BV resistance by targeting proto-oncogene MET, TIE2-expressing macrophages, and VEGFR2. In the GSC17 glioma xenograft model, administration of a combination of altiratinib and bevacizumab significantly prolonged survival compared with treatment using bevacizumab alone, suggesting that Altiratinib could be used to improve bevacizumab therapeutic efficacy (Piao et al., 2016).

SapC-DOPS (Saposin, BXQ-350), which is under development by Bexion Pharmaceuticals, is made of SapC introduced in DOPS nano-vesicles. It is thought to trigger anti-tumor activity by targeting phosphatidylserine present in large quantity in the outer membrane of tumor associated vasculature and by preventing TGF-β expression and tumor coagulation (Blanco et al., 2015). Mice xeno-grafted with U87 glioma cells, which received intravenous injection of SapC-DOPS, displayed tumor growth delay compared with mice treated with DOPS (Blanco et al., 2015). In another study, mice bearing intracranial U87ΔEGFR-Luc and X12v2 glioma received intravenous injection of SapC-DOPS, resulting in full tumor disappearance 250–350 days following drug injection among 25–75% of treated mice (Wojton et al., 2013). Interestingly, SapC-DOPS could also be conjugated with Gd (Winter et al., 2015), or with iodine-127 or iodine-124-fluorescent markers (Blanco et al., 2016), to image GBM tumors.

VB-111, which is under development by VBL Therapeutics, consists of a non-replicating Adenovirus, which specifically targets endothelial cells within tumor vasculature (Gruslova et al., 2015). Rats and mice bearing U87MG and U251 tumors, respectively, which received a single dose of VB-111, were shown to live slightly longer (a few days) than untreated animals (Gruslova et al., 2015).

TC-A237 (Alisertib) is under development by Takeda Pharmaceuticals Internationals that bought Millenium, which originally filed the patent protecting Alisertib. Alisertib acts against the tumor by inhibiting Aurora-A kinase. Mice bearing GB169 or GB30 glioma xenografts received orally TC-A237, resulting in an increased maximum survival by 5–15 days (Van Brocklyn et al., 2014).

Kinase Inhibitor Against GBM Tested Pre-clinically

GDC-0084, under development by Genentech and Kazia Therapeutics, is a brain penetrant inhibitor of PI3K and mTor. When it was orally administered to mice bearing U87 MG glioblastoma, it led to significant tumor volume decrease, but given the absence of survival curve in this study, it is difficult to conclude about the disappearance (or not) of the tumor (Heffron et al., 2016).

Immunotherapies

Immunotherapy seems to be the therapeutic approach, which brings the most important amount of hope to yield efficient GBM treatment. It has therefore become the most studied one. The number of clinical trials testing immunotherapies against GBM has increased from 3 in 1999 to 9 in 2015 (Calinescu et al., 2015). At the same time, there has been a real surge in the number of publications related to this topic (from 15 in 1999 to 164 in 2017 according to pubmed). The reader is redirected toward the large number of excellent reviews on this topic (Calinescu et al., 2015; Binder et al., 2016; Desaia et al., 2016; Hodges et al., 2016; Kamran et al., 2016; Dunn-Pirio and Vlahovic, 2017; Farber et al., 2017; Lyon et al., 2017; McGranahan et al., 2017; Miyauchi and Tsirka, 2017; Sahebjam et al., 2017; Tivnan et al., 2017), providing details about current or past clinical trials (Binder et al., 2016), and the different modes of action of these treatments (Calinescu et al., 2015; Curry and Lim, 2015).

Active Immunotherapy (Vaccine) Tested Clinically

Rindopepimut (Rintega, CDX-110), under development by Celldex, is a vaccine composed of peptides. It was designed

to treat patients expressing a mutant of EGFR (EGFRvIII), which is present among 20–30% of GBM patients and is absent on healthy cells. Rindopepimut should therefore specifically target GBM cells. It operates by triggering humoral and cellular responses against EGFRvIII-positive cells (Babu and Adamson, 2012). Mice bearing B16-msEGFRvIII tumors were treated with antibodies acting against EGFRvIII (Y10) with antitumor mechanism equivalent to that of CDX-110. They displayed a maximal survival day, which was 100 days larger than untreated mice, but this improvement was only observed for intra-tumor injection. Intravenous (IV) injection failed to increase mouse survival (Sampson et al., 2000). At first, phases I and II clinical trials carried out on GBM patients vaccinated with Rindopepimut seemed to suggest larger progression-free and overall survival times on patients expressing EGFRvIII than on those missing EGFRvIII (Schuster et al., 2015). However, this result was not confirmed in a phase III clinical trial, carried out on 745 GBM patients expressing EGFRvIII, which were first treated by maximal surgical resection and chemo-radiation. Indeed, this trial led to an overall survival, which was similar at 20 months for patients treated with CDX-110 and TMZ and those receiving TMZ alone (Weller et al., 2017).

SurVaxM, under development by MimiVax, is a peptide vaccine that targets survivin, a protein responsible for glioma cell survival, which is present among 95% of GBM patients. A first in man study carried out on patients with recurrent GBM demonstrated the safety and immune response induced by the vaccine and suggested an apparent increase in PFS and OS by 8 months and 56 weeks, respectively, compared with patients receiving chemotherapy (Fenstermaker et al., 2016).

Prophage (G-100, G-200, Vitespen), under development by Agenus, is a clinical vaccine containing a heat shock protein peptide complex (HSPPC-96), in particular the heat shock protein gp96. It is a patient specific vaccine fabricated using patient's tumor tissue. It is expected to trigger an anti-tumor immune response, possibly involving $CD8^+$ and $CD4^+$ T cells, as was observed during the prophage treatment of wild type Balb/c mice bearing fibrosarcoma tumors (Chakraborty et al., 2016). In a phase II GBM clinical trial, patients treated with Prophage and SOC (radiation and TMZ) displayed an increase in PFS and OS of 10 and 8 months, respectively, suggesting clinical efficacy. However, efficacy still needs to be confirmed on a larger cohort of patients (Chakraborty et al., 2016).

Gliovac (ERC 1671), which is under development by Epitopoietic Research Corporation (ERC), is composed of autologous antigens, surgically removed from patient's tumor tissue, which are administered together with allogeneic antigens coming from glioma tissues resected from other GBM patients. A phase I study showed that 100% of patients treated with Gliovac were still alive 6 months following the beginning of treatment compared with only 33% for the controlled group (Schijns et al., 2015). This suggests clinical efficacy of Gliovac, which is currently further investigated in a larger clinical phase II (NCT01903330).

IMA950, which is under development by Immatics Biotechnologies, is an immunotherapeutic multiple-peptide vaccine, specifically developed to treat GBM. It contains tumor associated peptides (TUMAP) found on human leukocyte antigen (HLA) surface receptors coming from primary human GBM tissue. It is designed to activate cytotoxic T cells against tumor cells expressing TUMAP and also to prevent potential tumor escape mechanisms. A phase I clinical trial carried out on HLA-A*02 positive patients seems to have highlighted an anti-tumor immune response, but it did not conclude in any increased survival (Rampling et al., 2016). Further studies therefore seem necessary to examine the potential therapeutic benefit of this vaccine.

DCVax-L, which is under development by Northwest Biotherapeutics, seems to be the most advanced dendritic cell (DC) vaccine. It contains a combination of autologous tumor antigens with patient's own antigens. Following injection to the patient, DCVax-L should enable DC to present their surface tumor antigen to the CD4 and CD8 T cells and hence to activate these immune cells specifically against the tumor. A clinical phase I/II showed that patients treated with DCVax-L displayed OS and PFS, which were longer than those of the historical control by 21 and 15 months, respectively (Polyzoidis and Ashkan, 2014). A phase III is currently ongoing to further confirm (or not) a therapeutic benefit.

Passive Immunotherapy (Anti-body Based) Tested Clinically

Depatux-M (ABT-414), which is under development by AbbVie, is an antibody-drug conjugate that preferentially binds to EGFR, which is overexpressed in glioma cell and present in 50% of GBM patients. It then internalizes in cancer cells where it releases an anti-microtubule agent, called monomethyl auristatin F, MMAF, triggering tumor cell death. In a phase I clinical trial, ocular toxicity was observed and it is too early to conclude about any clinical efficacy of Depatux-M (Van den Bent et al., 2017).

Asunercept (APG101, CAN-008), which is under development by Apogenix, is designed to block CD95 pathway by inhibiting CD95 ligand, which consists of the CD95 receptor extracellular domain fused to the Fc domain of IgG. A phase II clinical trial carried out on 91 patients suffering from recurrent GBM showed that APG101 administration combined with radiotherapy increases patient PFS and PFS6 by 2 and 17%, respectively, compared with radiotherapy alone (trial: NCT01071837). This suggests that APG101 leads to survival benefit, but this result still needs to be confirmed on a larger cohort of patients within a phase III clinical trial (Wick et al., 2014).

MEDI-3617 and MEDI-575, which are under development by MedImmune, are novel anti-PDGFRα antibodies. In mice bearing GL261 or U87 tumors, MEDI1317 was shown to increase mouse survival only when it was combined with cediranib (Peterson et al., 2015). In a phase II clinical study involving 56 patients with recurrent GBM, the administration of MEDI-575 was shown to be well tolerated but did not result in any significant clinical activity (Phuphanich et al., 2017).

Passive Immunotherapy (Check Point Inhibitor) Tested Pre-clinically

NOX-A12, which is under development by Noxxon Phama AG, is an anticancer agent that neutralizes CXCL12 blocking CXCL12

signaling through its two receptors, CXCR4 and CXCR7. Rats bearing brain tumors induced by injection of carcinogen ENU had a maximal survival, which was up to 150 days longer when they were injected with NOX-A12 compared with untreated rats (Liu et al., 2014). Mice bearing G12 glioma tumors, which were treated with a combination of bevacizumab and NOX-A12, were shown to live ∼15 days longer than those treated with NOX-A12 alone (Deng et al., 2017).

Nanotherapies

Nano-Therapy Tested on Human

Nanocell, which is under development by EnGeneIC, is composed of a minicell containing doxorubicin, which is conjugated with bi-specific proteins that target EGFR overexpressed in glioma cells. In a first in man study, signs of toxicity were not reported but efficacy has not yet been assessed (Whittle et al., 2015).

Nano-Therapy Tested *in vitro*

Gold Nanoparticles, which are under development by Midatech Pharma, are 2 nm Au NPs, coated with sugar moieties and/or thiol-polyethylene glycol-amine (PEG-amine). They were shown to be chemo-radiosensitisers, i.e., to enhance the antitumor efficacy generated both by X-rays and chemotherapy *in vitro* (Grellet et al., 2017).

miRNA Targeting GBM Drug Tested on Humans

TargoMiR, under development by EnGeneIC, are micelles filled with miR-16, which target EGFR and are designed to counteract the loss of the miR-15 and miR-16 miRNA family, which is associated with tumor growth. First clinical results were reported for the treatment for the treatment of mesothelioma, but not yet for glioblastoma (Van Zandwijk et al., 2017).

Glioma Stem Cell Targeting Drug Tested Clinically

ICT-107, under development by ImmunoCellular Therapeutics, is an autologous dendritic cell vaccine pulsed with class I peptide from tumor-associated antigens (TAA) designed to target six different tumor associated antigens (TAA). A clinical study carried out on 21 GBM patients has reported larger PFS and OS in patients with increased expression of TAA as well as a decrease or absence of CD133 overexpressed on glioma stem cells in 5 patients following a second resection (Phupahnich et al., 2013).

Gene Therapy Against GBM Tested Clinically

TOCA511 combined with TOCAFC, which is under development by Tocagen, is a retroviral replicating vector (RRV), which leads to the permanent integration of RRV into the cancer cell genome, and encodes yeast cytosine deaminase, which further converts the antifungal prodrug 5-fluorocytosine (FC) into the anticancer drug 5-fluorouracil, hence mediating local tumor destruction. In mice bearing U87, Tu-2449, TOCA injection seemed to have resulted in tumor disappearance among 40–100% of treated mice, depending on tumor type, quantity of drug injected, and the combination (or not) of TOCA511 with TOCAFC (Ostertag et al., 2012; Huang et al., 2015; Yagiz et al., 2016; Hiraoka et al., 2017; Mitchell et al., 2017). The combination of TOCA511 and TOCAFC treatment was also tested in a phase I clinical trial on patient suffering from GBM, resulting in favorable safety profile and better OS compared with lomustine treatment (Strebe et al., 2016).

Virus as GBM Treatment Tested Clinically

ParvOryx (H-1PV), which is under development by Oryx GmBH, is an oncolytic virus designed to specifically target and destroy cancer cells. A phase I/IIa clinical trial carried out on GBM receiving H-1PV showed that H-1PV was well tolerated, crossed the BBB, spread through the tumor, and possibly triggered an antitumor immune response through antibody formation and specific T cell response. Patient survival seemed to have been prolonged, but a phase III clinical trial is necessary to confirm this result (Geletneky et al., 2017).

EARLY DIAGNOSIS

The symptoms associated with GBM include headache, seizure, memory losses, personality changes, motor weakness, visual symptoms, language deficit, increased intracranial pressure leading to nausea, vomiting, and cognitive impairment (Kondziolka et al., 1987; Chang et al., 2005). These symptoms often appear when GBM tumor is already quite large and difficult to treat. It therefore seems important to develop diagnosis methods that can detect GBM before the appearance of any symptom. By contrast to other cancers for which early detection is carried out on a regular basis over a large percentage of the population at risk, for example by using mammography for breast cancer or prostate specific antigen detection for prostate cancer, GBM is not currently screened in this fashion. Physical examinations can diagnose GBM by detecting focal, visual field, and cognitive impairments, but these symptoms are usually detected when the extent of healthy tissue destruction is already quite significant. Standard imaging techniques such as MRI, CT, and PET, are costly and possibly lack the sensitivity to detect GBM tumors of small sizes. Therefore, their regular use to screen the whole population has not yet been considered. To detect GBM, stereotactic biopsies require knowing precisely where the tumor is located and could be used to confirm the presence (or not) of GBM but with more difficulty for initial GBM detection. Other diagnosis methods are under development to detect GBM biomarkers at a molecular level, but the author is not aware of any breakthrough in this field and more efforts should probably be spent to develop new methods for early GBM detection.

PRECLINICAL MODELS

To carry out a successful clinical trial on GBM patients leading to significant efficacy, it seems essential to have first optimized the treatment pre-clinically. However, studies on animals bearing GBM cannot easily be performed for the following reasons. First, governmental regulations on animal experimentations have become more and more stringent and restrictive (Workman

et al., 2010). Second, GBM animal models are prone to a series of drawbacks such as too small GBM tumors in mice and rats, cell-line xeno-grafts leading to tumors being genetically different from a human GBM, patients derived GBM (PDX) growing with difficulty and yielding tumor inhomogeneity, human GBM being only grown on immune-deficient mice lacking full immune system, animal GBM reported to be different from human ones, large animals with naturally occurring GBM such as dogs being scarce and treated at a cost and level of sophistication approaching those met in a human. To overcome these drawbacks, it therefore seems necessary to test GBM treatments on several different animal models described in more details below.

Small Animals

Current preclinical mouse glioblastoma models are divided between xenografts (cell-line and patient derived) and genetically engineered models.

Mice

- **Glioblastoma cell line xenografts,** such as the commercially available GBM immortalized cell lines U87, U251, T98G, and A172, are usually relatively easy to grow, but these cell lines are reported to be quite different from a GBM of a human patient, being circumscribed, having different genotype (Huszthy et al., 2012), MHC and integrin expression (Huszthy et al., 2012), as well as lacking certain GBM features such as single-cell invasion, tumor necrosis, or microvascular proliferation (Mahesparan et al., 2003). Furthermore, they can usually only be xeno-grafted into immune-deficient mice such as nude, NOD/SCID, and NOD/SCID gamma mice, with a weakened immune system that cannot be fully activated against the tumor. Furthermore, the differences between cell line xenografts and human GBM should be taken into consideration for the development of a molecular targeting GBM treatment in which the GBM composition is essential. However, when the mechanism of antitumor activity involves the application of radiation (X-ray, proton, laser, magnetic field) and is of physical origin, the treatment may act relatively similarly on xeno-graft cell line than on other GBM models (Alphandéry et al., 2017a,b; Le Fèvre et al., 2017).
- **Patient-derived xenografts (PDX)** are GBM tumors grown orthotopically or subcutaneously on mice by administering either biopsied patient tumor tissue (Fei et al., 2010; Kim et al., 2016), or cultured tumor spheres (Kang et al., 2015). Compared with GBM cell line xenografts, PDX present the advantage of reflecting the genetic and histological features of patient's GBM tumor, in particular being prone to single-cell invasions and tumor angiogenesis (Wakimoto et al., 2011). However, PDX have also been associated to the following drawbacks: (i) only 10–20% of PDX can successfully be grown on mice (Huszthy et al., 2012), (ii) PDX can be relatively inhomogeneous, (iii) PDX are usually grown on immune-deficient mice and therefore do not fully reflect patient's antitumor immunity. Despite of these weaknesses, it was demonstrated that PDX generated from cultivated patient-derived GBM stem cells (neurosphere) could better represent the GBM of a patient than immortalized GBM cell lines (Patrizii et al., 2018). The reason for introducing PDX cell lines also comes from the fact that a number of studies reported antitumor efficacy using immortalized GBM cell lines without demonstrating antitumor efficacy on humans (Patrizii et al., 2018).
- **GBM genetically engineered mouse (GEM)** models involve mice in which certain genes have been inactivated to study genetic alterations involved in GBM tumor initiation and progression. Although GEM models can help understanding the role of tumor microenvironment (Charles and Holland, 2010), they yield different tumors from human GBM, and tumor growth cannot easily be controlled in GEM.
- **Syngenic mouse models** include chemically induced (GL261, GL26, CT-2A) or spontaneous (P560) GBM mouse models (Oh et al., 2014). These models use immune-competent mice and are thus suitable for analyzing potential anti-tumor activity of GBM drugs. However, it remains uncertain whether these GBM animal models truly represent human GBM.

Rats

Compared with mice, rats enable the growth of larger GBM tumors, which can be advantageous for the development of certain GBM treatments. However, these tumors are not genetically engineered and targeting of specific pathways associated with GBM can therefore not be studied with rats. Most frequent GBM rat models include:

- **C6 glial tumors** were originally produced 8 months following injection of MNU to rats. These tumors contain certain features of human GBM such as the presence of pleomorphic cells, tumor invasion into the surrounding brain, expression of genes involved in human GBM, such as PDGFb, EGFR, IGF-1, and Erb3 (Morford et al., 1997; Guo et al., 2003).
- **9L gliosarcoma**, originally grown on rats and collected 6–7 months after MNU administration, were used to develop GBM drugs, in particular drug transportation across the BBB (Khan et al., 2005) as well as MRI and PET imaging techniques (Bansal et al., 2008). They also possess common properties with human GBM such as mutated p53, overexpressed EGFR, the presence of cancer stem cell (CSC), and a certain level of immunogenicity when they are grown in Fisher rats (Barth and Kaur, 2009).
- **T9 rat glioma** is similar to 9L gliosarcoma (Barth, 1998).
- **CNS-1 glioma**, originally produced by repeated MNU injections during 6 months, formed tumors with many common features with those of human GBM such as invasive growth, nuclear atypia, necrotic foci, macrophages, and T cells infiltration in the GBM tumor (Owens et al., 1998; Matthews et al., 2000; Nutt et al., 2001; Candolfi et al., 2007).
- **RG2 and F98 glioma**, originally produced by injection of ENU in rats, are highly invasive and overexpress PDGFb, Ras, and EGFR, representing well some of the behaviors of a human GBM (Weizsäcker et al., 1982). However, both tumors appear to be less immunogenic than human GBM (Tzeng et al., 1991).

- **BT4C glioma** initially developed by administrating ENU to pregnant rats, are characterized by dilated, non-uniform blood vessels, irregular nuclei, areas of high and dense cell proliferation (Stuhr et al., 2007), the presence in tumor periphery of a larger number of VEGF, tPA, uPA, and larger micro-vessel density (Barth and Kaur, 2009). This cell line was used to study the combination of VEGF inhibition with temozolomide and radiation (Sandström et al., 2008).
- **RT-2 glioma** was developed differently from the previously described cell lines, i.e., not through carcinogen exposure but using intracranial injection of Rous sarcoma virus in rats (Copeland et al., 1976). These tumors, which trigger a CD8+ immune response, may be used to study cancer immunotherapy.
- **A transgenic rat model** was developed by using the S100b promoter that led to the expression of a viral form of EGFR (v-erbB) (Ohgaki and Kleihues, 2005) and to the appearance of malignant glioma among a small portion of treated rats (Ohgaki and Kleihues, 2005; Yokoo et al., 2008). Although this model could be used, in particular to study glioma infiltration by tumor-associated macrophages (Sasaki, 2017), it requires further optimization to yield a larger percentage of rats with GBM.

Large Animals (Dogs)

In some respects, the dog GBM model appears more suitable for preclinical drug screening than the mouse or rat model. Indeed, the size of a dog tumor is closer to that of a human GBM. Furthermore, dog GBM models are possibly more representative of human GBM, with TP53, EGFR, PDGFRα, and IGFBP2 GBM markers being overexpressed in dog GBM, (Higgins et al., 2010), as well as cancer stem cell (CSC) and associated CD133 being present in dog GBM (Stoica et al., 2009). However, GBM are scarce in dogs with an incidence rate of only 7 per 100,000 dogs (Dobson et al., 2002). Animal experimentation on dogs also relies on the owner consent and leads to higher cost and more ethical issues than mouse or rat studies (Hansen and Khanna, 2004). GBM dog models were used to examine the efficacy of several GBM treatments such as: (i) immunotherapy by implanting stimulated autologous lymphocytes into the tumor bed (Ingram et al., 1990), (ii) brachytherapy by inserting an inflatable balloon (Iotrex) containing iodine-125 in the GBM resection cavity (Stubbs et al., 2002), (iii) gene therapy by administering a recombinant adenovirus to dogs, (iv) increased quantity of administered drug by using convection-enhanced delivery (CED) under the application of a pressure gradient (Dickinson et al., 2008).

DELIVERY OF THE TREATMENT

In order to reach efficient antitumor activity against GBM, treatments relying on physical and chemical mechanisms should both be improved.

Physical methods of GBM destruction, which rely on the use of previously described surgery, radiotherapy, lasers, or electric fields, combined with imaging, would most likely need to be sufficiently precise to image and remove GBM cells at the single cell level. This is not yet possible in the clinic, not only due to a lack of sensitivity of the current imaging and surgical tools, but also to part of GBM cells being located in difficult to access regions of the brain. Even if this became possible technologically in the future, debris of tumor cells, genetically modified DNA, RNA, or other tumorigenic biological material, could remain in the organism after treatment and trigger tumor re-growth. It therefore appears that these physical methods, which are essential to remove the large majority of the GBM tumor, should be combined with other therapeutic approaches acting at a more molecular level.

Most chemical treatments against GBM present the advantage of being specific, *i.e.* they target a specific part of the tumor, which is present or expressed in larger quantity in the tumor than in healthy tissues. Such targets include A2B5, CD15, CD44, CD71, CD90, CD133, Integrin-α6, L1CAM (Xu et al., 2015; Glaser et al., 2017), miRNA (Kim et al., 2016), EGFR, PDGFR, BCR-Abl, FLT3, VEGFR, P13K, mTor, Ras/Raf/MAPK, microtubule inhibitor, topoisomerase inhibitor (Laquintana et al., 2009; Oberoi et al., 2016), telomere repeat-binding factor 2 (TRF_2), MiR-21, MiR-125b, MiR-181, integrin such as $\alpha v\beta_3$ and $\alpha v\beta_5$ (Xu et al., 2015), tumor associated antigens (Platten et al., 2016), glioma stem cells (Hide et al., 2013). Although several GBM drugs have been shown to be able to interact with these targets leading to antitumor activity *in vitro* and/or in animals (Blanco et al., 2014; Paff et al., 2014; Thaci et al., 2014; Yang et al., 2015), most of them have not led to clear therapeutic benefit (Staedtke et al., 2016). This may be due to GBM drugs not efficiently reaching the tumor in humans, requiring GBM drug delivery to be improved to expect significant therapeutic activity on humans. The different routes of administration are described below.

- Oral is the easiest and most common route of administration, used for Mibefradil, TMZ, Curaxin, Altiratinib, MLN518, Enzastaurin, AZD2171, GDC-0084, and TC-A237. While several of these drugs (Curaxin, Barone et al., 2017, Altiratinib, Smith et al., 2015, GDC-0084, Salphati et al., 2016, TMZ, Agarwala and Kirkwood, 2000) were reported to cross the blood brain barrier, other ones were observed to be blocked by the BBB (MLN518, Oberoi et al., 2016, AZD2171, Oberoi et al., 2016) due to the presence of BBB efflux transporters. A clinical study compared TMZ oral and intravenous administrations, concluding that both routes lead to a similar level of drug exposure (Diez et al., 2010).
- Intravenous/intra-arterial route was used for Bevacizumab, ANG-1005, SapC-DOPS, and VB-11 administrations. These drugs crossed the BBB in different ways, i.e. by disruption of the BBB with mannitol for Bevacizumab (Boockvar et al., 2011; Burkhardt et al., 2012), through the low density lipoprotein receptor-related protein 1 (LRP-1) pathway for ANG-1005 (Bertrand et al., 2011), by binding to anionic phospholipid phosphatidylserine (PtdSer) for SapC-DOPS (Wojton et al., 2013). For BCNU, intra-arterial administration was reported to yield 50 times more drug in tumor tissue compared with intravenous injection (Tyler et al., 1986), indicating that this administration route may lead to a larger quantity of drugs in

GBM tumor than intravenous injection. Following treatment, intra-arterial delivery may also enable the neutralization with an antidote or removal by hemo-perfusion of drugs in excess (Dedrick et al., 1984; Oldfield et al., 1985), which could otherwise potentially yield side effects.

- Intradermal route essentially used to administer vaccine such as CDX-110, Gliovac, IMA950, DCVax-L, or ICT-107. This mode of administration is chosen for vaccine since the dermis and epidermis of human skin are rich in antigen-presenting cells, suggesting that it could favor an immune response (Hickling et al., 2011).
- Intratumoral route used for Gliadel and Panobinostat administrations. Intratumor administration presents the advantage of overcoming the problem of BBB penetration by enabling drug injection beyond the BBB, in or near GBM tumor cells. On the one hand, Gliadel, which is made of a chemotherapeutic drug (BCNU) embedded in a biodegradable co-polymer formed of 1,3-bis-(p-carboxyphenoxy)propane (pCPP) and sebacic acid (SA), is implanted in GBM resection cavity and progressively releases BCNU in the tumor (Bregy et al., 2013). Although Gliadel led to signs of efficacy (Bregy et al., 2013), they were accompanied by side effects including seizures and cerebral edema (Bregy et al., 2013). Therefore, the method of inserting drugs directly in the resection cavity requires further improvements to yield a better control on drug diffusion. On the other hand, Panobinostat is administered using another intratumor injection method under active development called convection-enhanced delivery (CED). In CED, the solution containing the drugs is pushed under pressure with a pump through one or several catheter(s) directly connected to the tumor. Advantages of CED come from the precise knowledge of the location where the drug is administered, the control over drug diffusion by adjusting the pressure with the pump, which enables interstitial delivery, the absence of injury caused by the catheters. CED was tested in a series of different clinical trials, leading to an acceptable safety profiles without however demonstrating any improved therapeutic efficacy (Vogelbaum and Aghi, 2015). CED therefore seems to require further refinement to be of added value for a GBM treatment.

ACCELERATED PROGRAM FOR GBM DRUGS TO REACH THE CLINIC/MARKET (ORPHAN DRUG STATUS)

An orphan status is given to a drug indicated for a rare disease, i.e., with an incidence lower than 5–7 per 10,000. Due to the relatively low incidence of GBM (5 per 100,000), GBM drugs are eligible to this status and most previously described drugs were given the orphan status by the regulatory agencies of various countries, most frequently by the EMA in Europe and FDA in the USA. This status was originally set up to encourage companies to develop treatments for rare diseases such as GBM for which the chances of generating a profit are undermined by the limited number of patients. Financially, it can provide: (i) partial coverage of clinical trial cost through tax credit reimbursement (50% in the USA and Japan, various percentages in Europe depending on the country), (ii) grants through programs that specially support orphan drug development (FDA and NHI in the USA, H2020 in Europe, NIBIO and AMED in Japan), (iii) discounts on regulatory fees necessary to obtain market authorization in USA, Europe, and Japan. In some countries like Japan, medical expenses can be covered by National Health Insurance in exchange of a control over drug price, a good system that enables both to lower drug development cost and to reach a reasonable drug selling price. Most importantly, the FDA and EMA grant a 7–10 years marketing exclusivity to an orphan drug in the USA and Europe, respectively, by not authorizing similar products to be commercialized during this lapse of time. The orphan status can also give access to scientific advice, which is provided by regulatory agencies to determine the right path toward clinical trials and commercialization and to avoid unnecessary costly and lengthy developments. Finally, it can lead to accelerated drug assessment and approval, which appear essential both to reduce drug development cost and to accelerate treatment access for GBM patients (Mariz et al., 2016). This status has been of enormous help to the pharmaceutical industry and it is uncertain that there would have been so many attempts to develop GBM treatments without it. However, it mainly relies on the seldomness of a disease. Indeed, among all drugs that received an orphan status by the EMA in 2010, Torisel reached the highest prevalence of 35 per 100,000 for the treatment of renal cell carcinoma (The Committee for Orphan Medicinal Products the European Medicines Agency Scientific Secretariat et al, 2011). The difficulty to develop a treatment and the severity of the targeted disease are two other essential criteria that should most probably be taken into consideration to maintain the orphan drug status to GBM drugs if/when GBM incidence increases in the future. The orphan status is also reserved to drugs and excludes medical devices. However, some medical devices, for example those of class III that are injectable and nano-formulated, may also deserve this status. This could ease the interactions between the pharmaceutical companies fabricating them and the regulatory agencies. An international authority could also be set-up to specifically manage/define the orphan drug status, enabling more uniform regulation and easier understanding of the implications of this status in the various regions of the world.

INTELLECTUAL PROPERTY

Concerning the field of tumor destruction by radiations such as X-ray, electric fields, or lasers, patents relate to different methods to image and then irradiate locally the tumor, to position the patient in the radiation field, to orientate and apply the beams toward the tumor, to measure and deliver the dose that can destroy the tumor while sparing healthy tissue, to produce a robotized irradiation system. With regard to surgery, we have identified patents on the Neuroarm robotic surgery system that allows to locally and precisely carry out tumor surgery while reducing the burden of tiring tasks for the surgeon. Anti-tumor drugs have been protected through various methods

for targeting certain specific cellular receptors such as EGFR or CD95, various drugs compositions or methods for drug production, formulation, or administration, various systems of drug transports through the BBB, inhibitors of protein kinase, antitumor vaccine comprising dendritic cells activated against the tumor, various immunogenic compositions containing for example heat chock proteins.

Next, some of the features of the patent landscape in the field of GBM treatment are underlined. The distribution in number of patents earned by companies to protect their therapy is presented in **Figure 3**. It shows a discrepancy between companies possessing a large number of patents that may be able to develop their activity independently and those that earn only one or even no patent and may therefore have to seek additional protections or to negotiate patent license agreements with other structures. Secondly, two relatively old and well-established drugs (Avastin and TMZ) are still the subject of intense patent filing, due to their status of already approved drug and to their modest efficacy against GBM. In this case, the strategy to seek additional and more extended in time protection on these compounds essentially consists in filing patents on combinatory treatments including them and on various new methods to prepare/administer/use them for cancer treatment.

A detailed but non-exhaustive list of patents that is representative of the different domains in which protection has been sought for is presented below.

- **3D-RT**: imaging of the irradiated region using various methods such as CT, PET, MRI, HIFU, video (WO1989008430, WO1991000057, WO2004047923, WO2008120117, WO2010109585, WO2010109586, WO2012119649, WO20130679), equipment for positioning the patient during RT (WO2005122993), determination of the dose that needs to be used during RT (WO2007084272, WO2011005862, WO2012129661, WO2015042727, WO2016066590, WO2016070721, WO2016081916, WO2017105024), robotic system to determine radiation beam trajectory during RT (WO2010120534), system to avoid collisions during treatment (WO2015017630), set-up of a quality assurance system to enable reproducibility of treatment parameters (WO2015044781), equipment to generate beams in several direction with modulated intensity (WO2015062093).
- **Cyber-knife:** Radiation equipment (WO199200644, WO2005000102), methods to orientate the radiation beam toward the tumor including being in some cases a robotized (WO2000054689, WO2002019908, WO2004044612, WO2006130771, WO2010030463, WO2011109668), system including in some cases a robotic arm for positioning patient (WO2005039472, WO2005099819, WO2006124434), linear accelerator (LINAC) including in some cases a robotic arm coupled to the LINAC (WO2009005556, WO2010085723), method for determining the volume to be irradiated and/or dose of radiation and/or treatment parameters (WO2006130862, WO2006120863, WO20070386062, WO2007117650, WO2008002374, WO2008005129, WO2008005132, WO2010065740), imaging methods and apparatus to irradiate tumor region (WO2007005445, WO2009114859, WO2010030397, WO2011156526), radiation system with a gantry to image and guide radiotherapy (WO2011106433, WO2012099747).
- **Gamma-knife:** method for collimation of radiation beams (WO1996019262), apparatus for positioning the patient (WO1997017896), method for determining radiation dose (WO1998057705), X-ray/gamma ray radiation apparatus with/without linear accelerator with/without collimator with/without imaging system (WO1999034866, WO1999040759, WO2001011928, WO2001011929, WO2001013907, WO2002031837, WO2002049044, WO2003008986, WO200500498, WO2000018538, WO2005058419, WO2006013325, WO2006097274, WO2008141667, WO2009052845, WO2009056151, WO2009129817, WO2010006630, WO2010012983), surface mountable apparatus for combining radiation and imaging systems (WO2001012066), stereotactic apparatus for guiding radiotherapy (WO2001021085), method for controlling/direction radiation beams (WO2005051215), method for treatment planning (WO20091182021, WO2017109680), method for fixing patient's head during radiotherapy (WO2009129847), method to enable patient movement during radiation (WO2009137010), method for measuring radiation (WO2010031452).
- **IMRT:** Methods for treatment planning (WO2003099380, WO2011154853), apparatus for sequential generation of modulated beams (WO2004087254, WO2004098712, WO2015062093, WO2017070433), dose determination for IRMT (WO2005052721), method for focusing several beams during IRMT (WO2015176265), support system for patients (WO2009033035), IMRT combined with VMAT (WO2011042819).
- **Stereotactic radiosurgery:** Apparatus for SRS (WO1989005171, WO1994023663, WO1996041349, WO1997035641, WO2001076480, WO2017134582), laser or other marker for aligning SRS beam (WO1996039228, WO2016162784), dose estimate for SRS (WO1990014129, WO2005052721), patient positioning device for SRS (WO2014066108, WO2015030379), collision prevention system for SRS (WO2017007165).
- **Optune:** Method for treating a tumor with an electric field oscillating at different frequencies alone or in combination with other treatments such as photodynamic therapy (WO2005115535, WO2007039799, WO2008087489, WO2009044289) for treating tumor cells.
- **Neuroblate/Visualase:** MRI guided surgical apparatus that includes a laser that heats the tumor (WO2003051217).
- **Neuroarm:** Robot for brain surgery (WO2009037576, WO2009040677, WO2009044287).
- **ABT-414:** Composition comprising antibody against Epidermal Growth factor receptor (EGFR) that inhibits Bcl-xL (WO2017214282, WO2017214301, WO2015143382, WO2017214233); composition comprising antibody drug conjugates with specific drug/antibody ratio (WO2014152199).
- **Afatinib:** Preparation of various forms/compositions of Afatinib or Afatinib di-maleate (WO201221174,

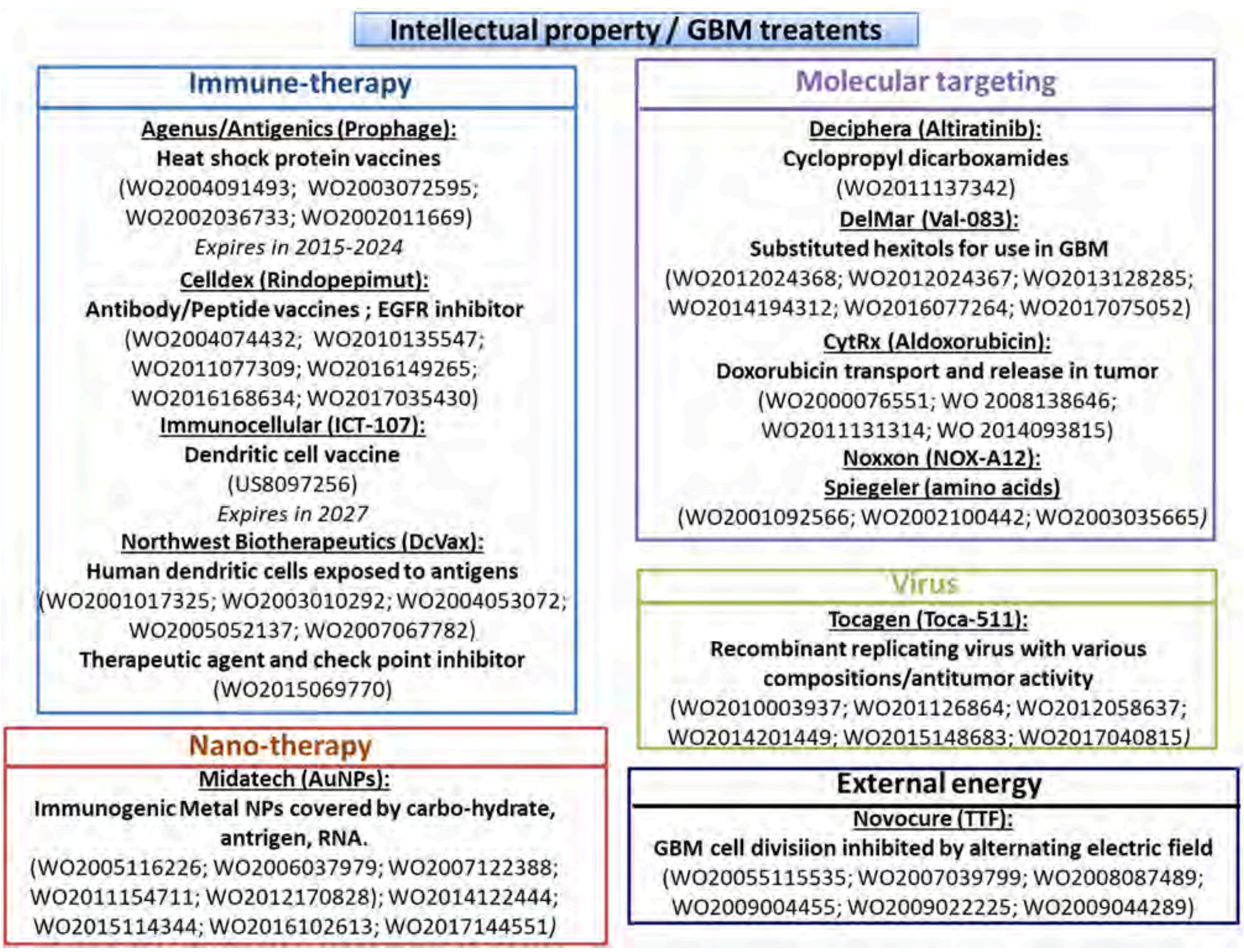

FIGURE 3 | Patents submitted by the various companies developing or commercializing GBM treatments. On the one hand, since the GBM treatment name is often not mentioned in patents, it is possible that the number of patents is underestimated in some cases. On the other hand, since some of the listed patents have a broad scope, it may happen that they only partly cover the field of a specific GBM treatment, possibly leading to an overestimate in the number of patents in some cases.

WO2013052157, WO2015007206, WO2015103456, WO2015186065, WO2016001844, WO2016027243, WO2016051380, WO2016079313, WO2016199076, WO2017033107, WO2017064039, WO2017093789, WO2017141271), use of Afatinib for cancer treatment (WO2015144934, WO2015153866, WO2016023822, WO2016027243).

- **Aldoxorubicin:** System of transport of a drug, in which a protein attached to the drug targets a tumor and specifically releases the drug in the tumor under pH changes, (US738777, WO2011131314), various formulations of doxorubicin (WO2008138646, WO201409381).
- **Altiratinib:** various kinase inhibitors (WO2007008917, WO2008033999, WO2013134298), derivatives of cyclopropane/cycloproply amides (WO2010051373, WO2011137342), pyridine/pyridine/pyrimidines derivatives (W02011139891, WO2013078295, WO2013134243, WO2013134252, WO2014145025, WO2014145028, WO2014145029, WO2015069266, WO20160661228, WO2014145004), imidazoline derivatives (WO2014145015), triazol derivative (WO2014145023), with anti-proliferative activity.
- **ANG-1005:** Pharmaceutical composition comprising aprotinin fragments Angiopep-1, Angiopep-2, conjugated (or not) to other compounds such as iduronate-2-sulfatase combined (or not) with lysomal enzyme, where this complex can cross the BBB and in some conditions accumulate in lysosomes (WO2007009229, WO2010142035, WO2013078562, WO2013078564, WO201385235, WO2014194427, WO2014194428, WO2016090495), paclitaxel, and a tonicity, buffering, bulking, solubilizing agent (WO2009127072).
- **Asunercept:** Cancer treatment with an inhibitor of CD95/CD95L in combination (or not) with an immunotherapeutic agent (WO2015107105, WO2015165973, WO2015197874, WO2017009429, WO2017051002).

- **Au NPs:** Metal nanoparticles with various ligands, mainly immunogenic ones (WO2005116226, WO2006037979, WO2007122388, WO2011154711, WO2012170828, WO2013034726, WO2013034741, WO2014122444, WO2014125256, WO2014135840, WO2015114341, WO2016162495).
- **AZD-2171:** Production of anti-angiogenic drug (WO20050004871, WO2005004872), composed of maleate (WO2005061488), modulating the activity of p53 kinase (WO2006014290, WO2006081034), in combination with gemcitabine (WO2007003933), Mek-inhibitor II (WO2008125820).
- **Bevacizumab (BV):** BV in combination with various treatments such as ZD6474 (WO2008037996), campthotecin (WO2010043050), carbonic hydrate (WO2013130354), pyradizanie derivatives (WO2013139423), a parvovirus (WO2016128146), AMP (WO2017045595), immune-conjugates that bind to FORLI (IMGN853) and doxorubicin (WO2017049149), ultrasounds (WO2017080481); BV administration method to increase BV penetration in the brain (WO2011049906); BV preparation with enhanced stability comprising buffering agent and osmotic pressure regulator (WO2016045570).
- **CBL-0137:** Method of production of CBL-0137 and use for cancer treatment (WO2015157172).
- **CDX-110:** Fabrication and use of antibody vaccine that preferentially binds to GPNMB, MET, EGFR, ALK (tyrosine kinase receptor), and induce immune antitumor activity (WO2004074432, WO2010135547, WO2016149265, WO2016168634), peptide-vaccine composition containing KL-H-peptide conjugate (WO2011077309).
- **DCVax-L:** Method to increase class I presentation of antigens by human dendritic cell (DC) (WO2001087325), methods to isolate, cultivate, differentiate DC precursor to form immature and/or mature DC preferentially to trigger T1 immune response (WO20030110292, WO2004072262, WO2004076651, WO20067067782, WO2017004230, WO2017048875, WO2003022215, WO2003095668), tangential flow filtration method to remove and isolate leukocyte from patient's blood (WO2004000444), composition comprising dendritic cells for administration to a patient (WO2004053072).
- **Enzastaurin:** Use of Enzastaurin in combination with HDAC inhibitor to treat cancer (WO2010074936).
- **GDC-0084:** phosphoinostide/pyrimidine kinase inhibitor and use for anticancer treatment (WO2007127183, WO2009042607).
- **Gliadel:** Carmustine alone or in combination with other drugs, with/without specific solvent, lyophilized or not, for cancer treatment (WO2003049743, WO200811960, WO2016077406), system for releasing carmustine in the brain using wafer/implant (WO2008013709, WO2016095592).
- **Gliovac:** Tumor vaccine comprising allogenic or xenogeneic tumor cells (WO2007085648).
- **H1-PV:** Method of tumor treatment using the parvovirus H1PV (US20120237483, WO2011157447, WO2012052158, WO2016206807, WO2016206844).
- **ICT-107:** Method of cancer treatment by dendritic cell vaccination comprising tumor associated antigens (US8097256, WO2014127296).
- **IMA950:** gp96 carrying antigens to activate DC (WO2002004516), or tumor associated peptides with/without tumor-associated T-helper cell peptide epitotes derived (or not) from survivin, preferentially binding to MHC-I (WO2003102023, WO2004085461, WO2005076009, WO2005116051, WO2009015841, WO2009015842, WO2009015843, WO2009138236, WO2010037513, WO2010037514, WO2015018805, WO2016102272, WO2016146751, WO2016156202, WO2016156230, WO2016170139, WO2016177784, WO2016202963, WO2016207164, WO2017001491, WO2017005733, WO2017009400, WO2017021527, WO2017060169, WO2017097602, WO2017097699, WO2017108345, WO2017140897, WO2017148888, WO2017157928, WO2017157972, WO2017174645, WO2017202806), generating immune antitumor activity.
- **MEDI-3617 and MEDI-575:** antibody association with sucrose to prevent antibody self-association (WO20122003470).
- **Mibefradil:** Method of preparation of Mibefradil (WO1998049147, WO1998049148, WO1998049149), anti-metastatic activity of Mibefradil (WO2005086971).
- **Nanocell/targoMir:** Method for purifying bacterial minicells (WO2004113507), method for targeting mammalian cells with minicells (WO2005079854, WO2006021894, WO2009027830), minicells brain tumor targeting (WO2013088250), combined treatment with minicells and interferon-gamma (WO2015049589).
- **NOX-A12:** Spiegelmer, in some cases immobilized (WO2001092566, WO2003035665).
- **Prophage:** Composition comprising a heat shock protein and a saponin or an antigen (WO2002011669, WO2004091493).
- **SapC-DOPS:** Composition comprising combination of saposin C and dioleoylphosphatidylserine for tumor treatment (WO2004096159).
- **SurVaxM:** surviving peptide vaccine for tumor treatment (WO2000003693, WO2006081826, WO2007036638, WO2007039192, WO2009012460, WO2009138236, WO2014153636, WO2016179573).
- **TC-A237:** Combination of Mek and Aurora inhibitors (WO2012167247).
- **TMZ:** Combined antitumor treatment with TMZ and ATase inhibiting agent (WO1994015615), Cisplatin (W01997007804), interferon (WO1997012630, WO2001052882), immunocytokine (WO20100078916), VEGFR2 (WO2010093771), methoxyamine (WO2001012199), irinotecan (WO2001054678), thalidomide (WO2002043720), TNF-ALPHA (WO2006026348), kinase inhibitors (WO2007033374, WO2008094484), bormeol and/or methol (WO2008022535), TMZ administered in microcrystalline suspension (WO2000033823), cancer treatment method with TMZ (WO2000057867), methods for TMZ synthesis (WO2002057268, WO2002057269), controlled release system containing TMZ (WO2004028534),

various formulations/compositions of TMZ and TMZ derivatives (WO2005063757, WO2006024238, WO2006032190, WO2008111092, WO201040168, WO2011036676, WO2012013116, WO2014091078, WO2014104671, WO2015062481), various method of TMZ protocol/administration/dosage for cancer treatment (WO2006060464, WO20080002544, WO2008038031, WO2008140724, WO2011072240, WO2011077458).

- **TOCA-511:** Formulation containing 5-fluorocytosine and/or retroviral vectors with immune-stimulating activity for cancer treatment (WO2010002937, WO2010148203, WO2011126864, WO2012058637, WO2014201449, WO2015021077, WO2015148683, WO2017040815).
- **Val-083:** Various derivatives of hexitols for cancer treatment alone or in combination with other drugs (WO2001091741, WO2012024367, WO2012024368, WO2013110058, WO2013128285, WO2014004376, WO2014194312, WO2016077264, WO2016183331, WO2017042634, WO2017075052, WO2017091588).
- **VB-111:** Fas-chimera adenovirus vector for cancer treatment (US9200056).

FIGURE 4 | A schematic diagram presenting the GBM community fighting against GBM, at the heart of which lie the patients.

THE DIFFERENT ACTORS TACKLING GBM DISEASE

At the heart of the GBM community lie the patients. Different structures contribute to the effort for the development of an effective GBM treatment. They consist of medical teams and hospital services dedicated to GBM treatment, EANO and SNO associations that organize conferences on glioblastoma and various means of communication within the glioblastoma community, patient associations, foundations, pharmaceutical companies, regulatory agencies, and various public and private structures that provide funding for research and clinical trials (**Figure 4**).

GBM TREATMENT COST

GBM costs can be divided between direct costs due to stays and treatments carried out at hospital and indirect costs coming for example from work leave and resulting income losses. In the United-States, GBM average direct cost per patient has been estimated as 8,500 $ per month, mainly coming from surgery, imaging, and radiotherapy, while standard chemotherapy only represents 0.1% of this cost (Cagney and Alexander, 2017). Direct costs have been shown to strongly depend both on country, varying from an average of 27,000 $ per patient in Sweden to 95,000 $ per patient in the United-States (Raizer et al., 2015), and on the type of given care, for example being less expensive using brachytherapy (23,000 $/patient) than external beam therapy (33,000 $/patient) (Raizer et al., 2015). Importantly, indirect GBM costs are usually reported to be much higher than direct ones, being 101,000 $/patient in Sweden (Raizer et al., 2015) and 112,000 $/patient in Spain (Undabeitia et al., 2018). Another important issue relates to treatment benefit relative to its cost. This can be evaluated by measuring the so-called incremental cost-effectiveness ratio per life of year gained (LYG). For cancer an acceptable average threshold has been set at 50,000 $/LYG (Raizer et al., 2015). For glioblastoma, which are extremely difficult to treat, this threshold is often exceeded, yielding 70,000 $/LYG for TMZ, 115,000 $/LYG for carmustine wafer, and 550,000 $/LYG for TTF (Raizer et al., 2015; Cagney and Alexander, 2017). Whereas, such high costs may be justified for TMZ and TTF, since both of these treatments increase PFS by 2 and 4 months, respectively (Stupp et al., 2005; Cagney and Alexander, 2017), it does not seem to be the case for carmustine wafers that have not demonstrated survival benefit and produce severe side effects (Bregy et al., 2013). Bevacizumab was also reported to lack cost effectiveness for treating GBM patients (Kovic and Xie, 2015).

MARKET

GBM market was estimated as 465 million $ in 2016 and is expected to reach 1 billion $ by 2025, being equally distributed between the United States, Europe, and Asia and the rest of the world (Glioblastoma Multiform market 2024, GBM Industry Research Report, Hexa research, California, United-States).

ANALYSIS OF COMPANIES DEVELOPING GBM TREATMENTS

Table 3 summarizes financial information concerning the various companies developing GBM therapies. Financial analysis has been carried out on companies that devote a substantial part of their activity to developing a GBM treatment, i.e., companies that mention GBM as therapeutic target in their 2017 annual report. Sixty percent of these companies fall within the category of small businesses (<100 employees), a quarter of them are of medium

TABLE 3 | Financial information concerning the various companies developing or commercializing GBM treatments, extracted from the 2017 annual report of these companies.

Co name	Year founded	Location (HQ) 2016	Revenue (MS, 2016)	Net income/Loss (MS, 2016)	Accumulated losses (MS)	No. of employees 2016	R & D (% GBM) (MS, 2016)	Gal & Admin (MS, 2016)	Market value (MS, 2018)
Agenus	1994	Lexington (USA)	22	−127	905	255	94 (8% GBM)	33	516
Celldex	2005	Hampton (USA)	7	−128	719	210	103 (10% GBM)	36	317
CytRx	1985	San Francisco (USA)	0.2	−51	416	27	36 (<10% GBM)	16	243
Deciphera Pharma	2003	Waltham (USA)	0	−12	176	42	14 (<15% GBM)	4	57
DelMar Pharma	2009	Vancouver (Canada)	0	−9	41	4	5 (100% GBM)	3	23
Elekta	1972	Stockholm (Sweden)	11	0.1	N.A.	3,600	0.15 (>50% GBM)	0.09	N.A.
Immuno-cellular	1987	Los Angeles (USA)	0	−27	96	7	19 (100% GBM)	5	4.2
Midatech	2000	Oxford (UK)	6.4	−20	59	84	6.7 (15–30%)	9	22
Northwest biotherapeutics	1996	Bethesda (USA)	0.6	−80	715	15	60 (100% GBM)	11	N.A.
Novocure	2000	Jersey Isle	83	−131	520	450	41 (20% GBM)	51	N.A.
Noxxon	1997	Berlin (Germany)	0.083	−11	129	10	5 (<20% GBM)	4	12.3
Roche	1896	Basel (Switzerland)	54,000	8,825	NA	94,000	10,400 (<5% GBM)	NA	190,988
Tocagen	2007	San Diego (USA)	0.031	−28	156	61	21 (100% GBM)	6	215

The year of creation of these companies, the location of their headquarter, their revenues in 2016, their net incomes or losses in 2016, their accumulated losses since their foundation, their number of employees in 2016, their amount of spending in R&D in 2016 with the estimated percentage of this spending dedicated to GBM research, their administrative and general spending in 2016, as well as the market value of these companies in 2016, are indicated. The market value was estimated by multiplying the value of the share by the number of shares for each of these companies. The percentage of R&D spending dedicated to GBM research was estimated by dividing the number of GBM drugs by the total number of drugs developed/commercialized by each of these companies. This estimate relies on the analysis of the 2017 annual report of these companies, possibly not mentioning some drug developments, hence possibly leading to overestimate/underestimate of this percentage.

sizes (between 100 and 500 employees), and 15% of them employ more than 500 people. Only the large companies seem to generate revenues. For Elekta, this may be due to the development of a medical device (Gamma-Knife) with less stringent regulations than a drug, multiple possible uses on various indications, and a marketing approach relying on selling a therapeutic device only once to a hospital, hence significantly reducing costs of fabrication and selling prices compared with drugs. On the other hand, Roche sells Avastin, a drug against GBM that has already been accepted for commercialization and can therefore be sold without substantial additional investment. Despite of the financial success of these large companies, the treatments that they commercialize do not enable to treat efficiently GBM. More efforts in research and development (R&D) should therefore be spent to improve this situation. Today most R&D financial investment on new GBM treatments is carried out by small and medium size companies with a distinction to be made between those concentrating exclusively on GBM (Immuno Cellular, Tocagen, Northwest Biotherapeutics, Del Mar Pharmaceuticals) and those with a more diverse portfolio of targeted indications (Agenus, Celldex, CytRx, Midatech, Novocure). These companies have been founded between 11 and 26 years ago, a lapse of time that has enabled most of them to reach clinical trials but was insufficient to yield business profitability. Indeed, all these companies incur losses, between 41 and 905 m$, and have a market capitalization that is lower than their accumulated losses. Furthermore, only Novocure seems to generate substantial revenues with its GBM treatment. This may be due to the relative efficacy of its Optune treatment observed in a phase III clinical trial carried out on GBM patients. Interestingly, our analysis does not lead to the conclusion that companies with a more diverse portfolio of targeted indications have a better financial situation than those mainly focusing on GBM. In fact, treatments against other cancers than glioblastoma may be less difficult to develop, but still require a significant amount of time and investment to reach commercialization, which opponently have not yet been reached by these companies. Our analysis further seems to suggest that development time, total financial investment, level of complexity, and benefit/risk ratio of the drug/medical device under development, are the parameters that determine if/when a company developing a GBM treatment can reach profitability.

CONCLUSION AND FUTURE PERSPECTIVE:

Glioblastoma is a very aggressive cancer, leading to patient death a few months only following diagnosis. For operable GBM, surgery remains the most effective initial GBM treatment. However, it does not enable the removal of the entire tumor and the tumor therefore re-grows.

GBM treatments that are under development or commercialized include:

- Methods to improve surgery, such as the maintenance of GBM patients awake during the surgical operation (AWC), the use of a robotized system enabling to improve surgery accuracy (Neuroarm), tools to improve visualization of tumor cells and enable a distinction between tumor and healthy cells using fluorescence imaging (PET, OCT, CLEM), magnetic imaging (iMRI, gMRI, MEG, nTMS), DTI-FT or MS.
- Techniques to improve radiotherapy, using an external X-ray source, which is combined with tumor imaging (IGRT, HT), modulation of radiation intensity (IMRT), a focalization of the radiation beam at some specific locations of the tumor (SRT, Gamma-knife, cyber-knife), an external source of protons enabling to limit the overlap of the radiation beam with the healthy tissue region (PRT), an internal source of X-rays (BT, RmAB, RS).
- GBM treatments using different electromagnetic radiation sources such as the electric field blocking the mitosis of tumor cells (Optune), or laser thermotherapy locally heating the tumor (Neuroblate, Visualase).
- Therapies targeting specific parts of the tumor (Mibrefadil, TMZ, Gliadel, Aldoxorubicin, Val-083, ANG-1005, Afatinib, CBL0137).
- Drugs against angiogenesis (Bevacizumab, Altiratinib, MLN518, SapC-DOPS, VB-111, Enzastaurin, TC-A237, AZD2171).
- A kinase inhibitor (GDC-0084)
- Immunotherapies such as vaccines (Rindopepimut, SurVaxM, Prophage, Gliovac, IMA950, DCVax-L), antibodies (Depatux-M, Asunercept, MEDI-3617 and MEDI-575), check point inhibitors (NOX-A12).
- Nanotherapies (Nanocell, AuNP)
- miRNA targeting (TargoMIR)
- Glioma stem cell targeting (ICT-107)
- Gene Therapy (TOCA511)
- Virus (ParvOryx)

Among these treatments, Optune seems to be the only one with some efficacy (although rather modest) demonstrated in a phase III clinical trial. Many of them are still at a too early stage of development to be able to firmly conclude about their efficacy.

Several ways to improve the efficacy of GBM treatments have also been suggested. Early diagnosis methods could be developed enabling the treatment of smaller tumors possibly easier to eradicate. More preclinical trials could be carried out on large animals such as dogs whose relatively large tumor sizes could lead to a better estimate of the human dose than mouse studies. Drug delivery could be improved to better enable GBM drugs to reach the tumor. For intravenous injection, new methods shall be developed to allow GBM drugs to cross the BBB. For intra-tumor administration, a better diffusion of the drug should be obtained, for example by using CED.

At an industrial level, the development of GBM therapies has been facilitated by the orphan drug status that applies on GBM drugs due to the low prevalence of GBM. Several analyzed companies seem to earn a large number of patents protecting their GBM treatment and may be able to generate revenues when/if they firmly demonstrate some efficacy with their GBM drug, as it is the case for Novocure that has announced a large revenue in 2016 (**Table 3**).

EXPERT OPINION SECTION

This review describes industrial developments of GBM drugs and medical devices at different stages of developments, i.e., which were tested in:

- early clinical trials not yet enabling to conclude about their efficacy on a large cohort of patients (ICT-107, VAL-083, Depatux-M, MgLITT, Prophage, APG101, Mibefradil, Nanocell, ERC-1671, IMA950, MEDI-575, Panobinostat, Survax-M, DC-Vax-M, Parvovirus, Gama knife).
- phases II or III clinical trials resulting in an absence of efficacy (Rindopepimut, Avastin, Gliadel, PSMA ADC, Trebanaib, Afatinib, Enzastaurin, Tandutinib).
- phase III clinical trials demonstrating some modest efficacy (Temozolomoide, Optune)
- pre-clinically mainly showing tumor growth retardation on tumors originating from PDX and/or immortalized cell lines (BiCNU, AV-0113, GMCI, AFM21, ANG1005, SapC-DOPS, Aldoxorubicin, Altiratinib, CBL0137, Selenexor, Indoximod, GDC-0084, NOX-A12, Parvovirus, Toca 511, VB-111).
- Cells showing decrease in GBM cell survival or proliferation (Crenolanib, KML001, TC-A2317)

Optune is the only recently developed GBM drug that has shown some efficacy (although rather modest) on a large cohort of patients.

Among the approaches tested for GBM treatments that have led to preclinical efficacy or clinical efficacy on a limited number of patients are:

- drugs targeting of various types of molecules such as T-type channel (Mibefradil), DNA (Aldoxorubicin, Val-083, CBL0137), microtubule (ANG-1005), EGFR (Afatinib),
- Anti-angiogenic drugs (Altiratinib, SapC-DOPS, VB-111, Alisertib,
- Kinase inhibitor (GDC-0084),
- Immunotherapies (Survax-M, Prophage, Gliovac, IMA950, DCVax-L, Asunercept, NOX-A12
- Nanotherapies (Gold nanoparticles)
- Glioma stem cell targeting (ICT-107)
- Gene therapy (TOCA 511 combined with TOCAFC)
- Virus (ParvOryx)

More clinical trials are necessary to determine if these drugs are efficient (or not) on a large number of patients.

Traditional approaches fail to treat efficiently glioblastoma. Surgery does not completely remove glioblastoma without damaging the brain. Radiation therapy cannot be used beyond a certain threshold dose, which is insufficient to completely eradicate glioblastoma. Chemotherapy has shown limited efficacy and can be very toxic.

According to the author, one of the most interesting therapeutic approaches is to expose the tumor to an external energy source, such as an alternating electric or magnetic field, to repeatedly induce antitumor activity. Ideally, these sources should be chosen to be able to carry out the treatment until the tumor has fully disappeared. They should also be sufficiently compact, inexpensive, and easy to use so that patients can carry out the treatment at home, possibly with the help of a nurse. Ultimately, it is desirable that the use of the hospital environment is minimized to reduce costs and allow the treatment of as many patients as possible at a reasonable cost for each patient.

Immunotherapy approaches have also raised an enormous interest, but failed until now to show antitumor efficacy on humans. This may be due to the complex immune mechanisms that are not yet fully described and understood. These approaches should be pursued, maybe by trying to reactivate the immune system against the tumor several times until the tumor has fully disappeared.

Finally, on the one hand more effort should be spent to develop a proper preclinical model, without which treatment efficacy cannot be properly assessed. On the other hand, methods should be developed to diagnose glioblastoma earlier. The author thinks that those steps are prerequisites to develop an efficient glioblastoma treatment.

AUTHOR'S NOTE

Due to the proximity of the author with the two companies Nanobacterie and Magforce, the latter are not analyzed in this review. The patents were quoted by their publication number.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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Conflict of Interest Statement: EA has been working with the company Nanobacterie.

GLOSSARY (NON-EXHAUSTIVE)

Allogeneic antigen, Antigen occurring in some but not all patients;

Anaplastic astrocytoma, tumors developing from brain cells called astrocytes;

Anaplastic ependymoas, tumor that forms when cells in the central nervous system (including the brain and spinal cord) begin to multiple rapidly;

Autologous antigen, Antigen belonging to the same organism;

Brain parenchyma, brain nervous tissue;

Cerebral edema, excess accumulation of fluid in the brain;

Cerebrospinal fluid, regulates the distribution of substances between cells of the brain;

Cortical, belongs to the cerebral cortex is the largest region of the cerebrum in the mammalian brain and plays a key role in memory, attention, perception, cognition, awareness, thought, language, and consciousness;

Dendritic cells (DC), Antigen-presenting cells whose function is to process antigen material and present it on the surface to T cells of the immune system;

Glial cells, cells consisting of microglia, astrocytes, and oligodendrocyte lineage cells as their major components, constitute a large fraction of the mammalian brain;

Hippocampi, parts of the brain responsible for memory;

Microtubules, Parts of the cytoskeleton of cells;

Oligdendroglioma, third most common type of glioma, comprising 4%–15% of all glioma, and classified by their degree of malignancy into grades II or III, according to WHO classification. Only 30% of oligodendroglial tumors have anaplastic characteristics;

Overall survival (OS), Percentage of patients who are still alive for a certain period of time after they were diagnosed with a disease or started treatment for a disease, such as GBM;

Platelet-derived growth factor receptors (PDGFR), Cell surface tyrosine kinase receptors of platelet-derived growth factors (PDGF), which regulate proliferation, differentiation, and growth of cells;

Progression free survival (PFS), Length of time following a treatment during which a disease does not worsen;

Ventricle, communicating network of cavities filled with cerebrospinal fluid (CSF) and located within the brain parenchyma.

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Tumor Treating Fields: Adjuvant Treatment for High-grade Gliomas

Patricia Anthony, Stacey McArdle, and Michele McHugh

Objective: *To introduce effectiveness of tumor treating fields (TTFields), how to care for the patient with this type of treatment, and the critical role the nurse plays in educating the patient about this innovative treatment.*

Data Sources: *Published research and articles in both nursing and medical journals.*

Conclusion: *TTFields are an antimitotic therapy delivered via transducer arrays that are worn on the scalp to treat newly diagnosed and recurrent glioblastoma, the most aggressive primary brain cancer. Oncology nurses are integral in educating and supporting the patient in its use and managing its of treatment.*

Implications for Nursing Practice: *Nurses are on the front line of educating the patient, caregivers, and the larger body of clinicians who deliver care to these patients. Education provided by nurses increases the patients' knowledge, and thus compliance, as well as the overall outcome through proper usage of TTFields.*

Key words: *tumor treating fields, compliance, portable device, electrical field.*

Glioblastoma (GBM) is the most aggressive and most common of all malignant central nervous system tumors, accounting for 47.1% of all primary malignant brain tumors.[1] GBM are most common over the age of 50, with rates highest in the 7th and 8th decades of life but can develop during any age, occurring in 3.2 per 100,000 population.[1] Supratentorial lesions are the most prevalent location for GBM to occur, followed by the cerebellum and then the spinal cord causing progressive neurological deficits, seizures, and behavioral and cognitive decline.[2] GBM remains an incurable disease with an average 2-year survival rate of 17.2% and 5-year survival rate of 5.5%.[1] For over a decade the widely accepted median survival has been approximately 15 months.[3,4] Recurrent disease has an average survival of approximately 9 months.[4] Several environmental and behavioral risk factors have been researched, with exposure to ionizing radiation

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being the only validated factor.[5] Historically, gliomas are classified by the World Health Organization (WHO) by tissue type, neuroglial cells, and clinical behavior. Unlike other cancer types, which are staged, gliomas are graded by their histologic appearance, with GBM being the highest at grade IV. GBM are differentiated by two subtypes that evolve via different genetic pathways. Primary or de novo GBM occur rapidly with a sudden onset of symptoms and do not arise from a pre-existing lower-grade tumor type. Secondary GBM arise from lower-grade glial tumors and are not as common but carry a better prognosis.

In 2016, the WHO restructured their central nervous system tumor classification to incorporate both tumor histology as well as defined molecular parameters.[6] This genome analysis assesses genetic losses, mutations, amplifications, and expression of specific genes or proteins in the tumor tissue.[6] Tumors that exhibit isocitrate dehydrogenase (IDH) mutations are more frequently associated with tumors that have progressed from lower-grade neoplasms, which may predict an improved prognosis. Consequently, the methylguanine methyltransferase promotor status is a protein that repairs damaged DNA. When methylguanine methyltransferase is silenced by methylation (methyl molecules are bonded to the DNA)[1] tumors are unable to repair the damage that has occurred by alkylating agents. Improved response to chemotherapy and radiation is seen with increased methylation status.[7,8] Glioma biomarkers will continue to develop the diagnosis of brain tumors and aid in tumor classification, prognostic value, and potential treatment response.[9]

Surgery, radiation, and chemotherapy remain the treatment paradigm for GBM. However, the infiltrating nature of this tumor and the protective attribute of the blood brain barrier make this tumor difficult to treat. Dating back to the late 1960s, studies have shown that maximal tumor resection and radiation therapy with supportive care of corticosteroids showed survival benefit.[10,11] Recent radiotherapy advances allow for more focused treatment techniques that have diminished treatment toxicity but have not changed the overall survival (OS) rate in high-grade gliomas.[7] In the last four decades the US Food and Drug Administration (FDA) has approved a limited number of drug therapies for the treatment of GBM. In 1977, intravenous carmustine was the first drug approved for palliative intent. Almost 20 years later, in 1996, the carmustine wafer was approved for recurrent disease and in 2003 for newly diagnosed patients following surgery; all with minimal effect on survival.[10] However, in 2005 a new treatment option became available for newly diagnosed patients. Temozolomide (TMZ) in combination with radiation therapy followed by monthly TMZ advanced treatment options and improved OS. The 2-year survival rate was significantly greater in the TMZ/radiation group compared with the radiation-alone treatment arm (26% *v* 10%, respectively).[4] Thus, this protocol has become the standard of care for treatment of GBM in the newly diagnosed patient. Recurrent disease options remain limited. In 2009, bevacizumab gained accelerated approval and FDA final approval in December 2017 for previously treated, symptomatic patients with GBM with progressive disease.[12] Over the past decade, 23 clinical trials have investigated drugs to combat GBM with failed success in extending survival.[13]

Tumor Treating Fields

With the lack of success with traditional treatment methods, in 2000 Professor Palti[14] began investigating the effects of different electrical frequencies and their effects on cell division of cancer cells as well as quiescent cells. His goal was to provide innovative cancer treatment without the debilitating systemic effects associated with traditional chemotherapy. As a result of this research, tumor treating fields (TTFields) was developed as a possible treatment modality.

TTFields interfere with the natural electrical properties of dividing cancer cells. The effect that an electric field has on tissue is directly related to the intensity and the frequency that is manifested. Higher frequencies generate heat and are seen in the use of radiofrequency ablation, whereas low frequencies are seen in cardiac pacemakers.[15] TTFields alter tumor cell polarity by administering low-intensity, alternating electric fields at an intermediate frequency (200) kHz. This treatment spares normal quiescent cells but directly affects cell polarity and suppresses cell proliferation in rapidly dividing cancer cells, ultimately causing apoptosis.[16] For normal cell division to occur, charged cellular protein, specifically septin and tublin, need to align at various stages of cell division (Fig. 1).[16] When an external force of an electric field is exerted on these polar molecules it

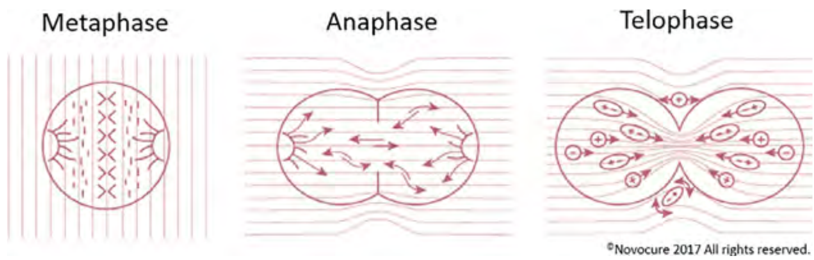

FIGURE 1. TTFields disrupts charged particles during the stages of cell division. During metaphase and anaphase the alternating electrical field disrupts the alignment of highly polarized tubulin subunits and impairs the assembly of spindle cells. Cells that change and escape mitotic arrest form a nonuniform electric field causing the charge particles to move to the cleavage furrow, not allowing cell division to occur and potentially leading to cell death (telophase). (Reprinted with permission of Novocure).

prevents them from aligning in proper formation and cell division is disrupted. TTFields target cancer cells at a rate of 100,000 to 300,000 times a second, altering these highly polar intracellular components and not allowing proper cell formation.[17,18] TTFields spare damage to healthy cells and target the rapidly dividing cancer cells.

Through the use of insulated electrodes worn on the scalp, TTFields delivers an electric field in two opposing directions. To increase the intensity of TTFields, optimal array layout, an individualized patient specific plan, is essential to achieve maximal treatment to the tumor area. One electric field study showed that adapting paired arrays to a specific configuration achieves the greatest intensity by the TTFields to the tumor.[19] The NovoTAL system (Novocure, Portsmouth, NH; Fig. 2) is an FDA-approved software planning system that certifies physicians to generate individualized plans for patients with gliomas. Based on anatomic magnetic resonance imaging (MRI) measurements, including size and location of the tumor, NovoTAL calculates the specific configuration for the array placement. The distribution of TTFields throughout the brain directly correlates with the type of tissue or bodily fluid it passes through, including bone, white matter, gray matter, and cerebral spinal fluid. The tissue type directly determines the electric field conductivity and distribution throughout the brain.[19] This data is uploaded via the software system to generate a map for each patient that is used as a guide for applying the transducer arrays. Physicians can update the configuration of the arrays as MRI changes occur to continue giving patients maximum benefit despite tumor alterations.

TTFields are delivered through the medical device Optune (Fig. 3). Considered durable medical equipment, this portable operating system

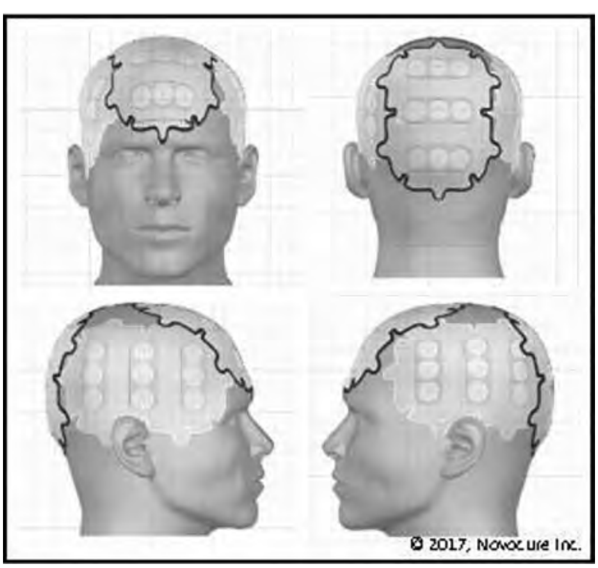

FIGURE 2. NovoTal mapping – individulized patient plan. (Reprinted with permission of Novocure).

FIGURE 3. TTFields are delivered through the Optune® medical device. (Reprinted with permission of Novocure).

consists of an electric generator, four insulated arrays, battery pack, charger, power cord, and carrying case. Each one-time-use transducer array is comprised of nine ceramic discs covered in hydrogel and attached by a flexible circuit board with adhesive tape. The array is plugged into the device box via a connection cable. When transducer arrays are connected to the power source and the power source is on, the device is delivering electrical fields, allowing for continual treatment. The original Optune system, used in pivotal clinical trials, weighed approximately 6 pounds and needed to be powered down and turned off before its battery could be changed. This process disrupted the delivery of TTFields. The second-generation system has a plug-in power cord that allows patients to change batteries without disrupting delivery of electrical fields. The current system weighs only 2.7 pounds, making it is easily transported and incorporated into daily living (Fig. 4).

Clinical Studies

In 2011, Optune became the only FDA-approved medical device to treat recurrent or progressive GBM based on the findings of the pivotal EF-11 clinical study. In the EF-11 clinical study, TTFields as monotherapy was studied against physician's choice chemotherapy.[20] TTFields were shown to be as effective as second-line chemotherapy, with improved quality of life (QoL) including emotional and cognitive functioning.

FIGURE 4. Patient wearing the portable Optune® device with carrying case. Pictured front to back and left to right: Transducer array, connection cable and box, power supply and cords, battery charger with batteries, portable field generator, and easy access sleeve bag. (Reprinted with permission of Novocure).

However, no difference was observed in OS (median, 6.6 months for TTFields *v* 6 months for chemotherapy).[20] TTFields are suggested to be equivalent to traditional chemotherapies commonly prescribed for recurrent GBM without the systemic side effects. This alternative treatment modality provides patients with recurrent disease another treatment option, especially for those who are unable to tolerate systemic therapy.

Following the success of the EF-11 clinical trial, the EF-14 multi-centered phase III, randomized trial focused on the efficacy of TTFields in combination with TMZ versus TMZ alone following completion of standard of care, radiation with TMZ, in newly diagnosed patients. There were 695 patients randomized with the primary endpoint being progression-free survival (PFS) and secondary endpoint as OS.[21] Additional predefined secondary endpoints analyzed were QoL and PFS at 6 months and 1 year.[21] All patient characteristics were balanced, including age, location of tumor, resection status, performance status, and molecular profile. Randomization occurred within 4 to 7 weeks of completion of radiation and TMZ. In 2015, TTFields gained expanded approval by the FDA for newly diagnosed patients based on a predefined interim analysis of 315 enrolled patients demonstrating significant improvement in PFS and OS.[21] In 2016, the National Comprehensive Cancer Network (NCCN) included TTFields as part of the standard-of-care treatment paradigm. It was given a 2A category of recommendation, meaning the intervention is an appropriate treatment option.[16]

The published findings of the final analysis data of the EF-14 phase III trial of all 695 enrolled patients were consistent with the planned interim analysis. The 5-year survival analysis confirmed significantly improved OS and PFS versus TMZ alone. OS rates for the combination of TTFields plus current standard of care versus standard of care alone were improved at 2 years (43% *v* 31%, respectively) and 5 years (13% *v* 5%, respectively) from randomization (Table 1).[13] Median OS from randomization for TTFields/TMZ was 20.9 months versus 16 months for TMZ alone. Median PFS was 6.7 months with TTFields/TMZ versus 4.0 months with TMZ alone. It is important to note that the significant OS was seen across all subgroups that used TMZ versus standard of care alone.[12] Patients who wore the device greater than 18 hours a day lived significantly longer

TABLE 1.
Summary of Final Analysis of the Randomized Clinical Trial of GBM Patients with TTFields Plus Maintenance TMZ versus TMZ Alone

Study Endpoints	Summary of Results
	Median follow-up of 40 months
Primary endpoint	Patients treated with TTFields plus TMZ (n=466) *v* TMZ alone (n=266)
PFS	Longer median (95% CI) PFS 6.7 months (6.1–8.1) *v* 4.0 months (3.8–4.4)
Secondary endpoint	Longer median OS 20.9 months (19.3–22.7) *v* 16.0 months (14.0–18.4)
OS	PFS 6 months: 56% (95% CI, 51%–61%) *v* 37% (95% CI, 30%–44%)
Exploratory endpoints	2 years: 43% (95% CI, 39%–48%) *v* 31% (95% CI, 25%–38%)
PFS 6-month survival	3 years: 26% (95% CI, 22%–31%) *v* 16% (95% CI, 12%–33%)
Annual survival rates, year	5 years: 13% (95% CI, 9%–18%) *v* 5% (95% CI, 9%–18%)
AEs	
Systemic AEs	The overall incidence of systemic AEs was not associated with an increase with TTFields/TMZ *v* TMZ alone (48% *v* 44 %)
	Medical site reactions had a higher incidence with TTFields/TMZ (52%)

Abbreviations: GBM, glioblastoma; TTFields, tumor treating fields; TMZ, temozolomide; PFS, progression-free survival; OS, overall survival; CI, confidence interval; AE, adverse event.
Adapted and reprinted with permission from Stupp et al.[13]

than those who wore it less than 18 hours a day.[13] Newly diagnosed patients with GBM with greater than 75% compliance have a 2-year survival of 43% in combination with adjuvant TMZ as compared with TMZ alone of 31%.[21] Most recent reports showed patients with a 90% or greater compliance have a 29.3% survival at 5 years and even in patients with as low as 50% compliance have improved outcomes.[22]

Adverse Events

Adverse events (AE) of TTFields plus TMZ are comparable with TMZ alone.[13] Side effects such as thrombocytopenia, nausea, constipation vomiting, fatigue, and headache were seen in both arms of the study. Although both grade 3 or 4 AEs were present in both study arms, none of the systemic grade 3 or 4 AEs were directly related to the wearing of TTFields.[13] Fifty-two percent of patients exhibited mild to moderate medical device site reaction with TTFields plus TMZ.[13] Because the most common reactions were skin-related AEs, further analysis was conducted to characterize these dermatologic events. Irritant and allergic contact dermatitis occurred with sensitivity to hydrogel, moisture, or reaction to tape. Mechanical irritation from shaving or pressure of the array disc had the potential to cause erosion or ulcer. Skin infection or pustules occurred from bacterial infection. Although mild to moderate skin irritation occurred, the dermatologic AEs were easily managed and reversible.[13,23,24]

Preventive management

Good skin preparation with each array change is important to prevent skin breakdown. However, if identified early, skin reactions can be easily managed, are reversible, and will not result in discontinuation of treatment.[13,24] Skin preparation and management of skin-related AEs are outlined in Table 2.

Preventing TTFields-induced skin irritation with proper scalp preparation is imperative. Patients are instructed to change transducer arrays 1 to 2 times per week, but more frequent changing may be required in warmer weather or with increased physical activity that leads to increased sweating.[25] Increased sweating, hyperhidrosis, may require patients to apply a topical aluminum chloride solution to the scalp during array changes. Hair growth rate may affect the need for re-shaving the scalp, warranting additional array changes.[23] Transducer arrays should be removed gently by slowly pulling back the edges, taking approximately a minute to remove each array. If the arrays are difficult to remove it is recommended to apply mineral oil to the array edges to loosen.[24] Caregivers should be instructed to evaluate skin condition for erythema or irritation with each array change and to notify the health care team immediately of any skin changes. Moving transducer arrays slightly (approximately

TABLE 2.
Management of Dermatologic Adverse Events

Type of Dermatologic Problem	Recommended Management
Preventive measures	Provide caregiver and patient education Educate on shifting arrays, changing the transducer arrays every 3 to 4 days or more frequently if needed (humid climate may produce moist skin) Educate on proper loosening of array adhesive to avoid skin damage Repetitive mechanical trauma, such as array changing and shaving of scalp, may irritate skin Assess patient skin prior to each array application Note areas of break down and condition of skin Avoid placing ceramic discs over areas of bony prominences, surgical scars, or areas that are irritated. May cut some of adhesive around the area or place non-adherent dressing over area and under adhesive but not under ceramic disc Clean hands and scalp prior before application to prevent infection Avoid use of tight, non-ventilated head gear Communicate with patients and reassess skin as needed
Dermatitis - skin inflammation with edema and erythema caused by allergic contact dermatitis from exogenous allergen or irritant contact dermatitis from direct chemical damage	Do not use in patients with known irritation or allergy to hydrogel or tape Irritation from hydrogel, adhesive, moisture, alcohol, or shaving can occur Always reassess skin every 2 weeks Grade 1: use high-potency topical corticosteriod ointments Grade 2: treat like a grade 1 but avoid direct contact of affected area. May need to hold therapy until a grade 1 Grade 3: treatment interruption and possible dermatology consult
Erosions - loss of portion of the epidermis	May result from repeated array removal, shaving, or ceramic disc pressure Always reassess skin every 2 weeks Grade 1: topical prescription-grade antibiotic ointment Grade 2: treat like grade 1 but add oral antibiotics. Avoid direct contact of affected area (may cut some of adhesive around the area or place non-adherent dressing over area and under adhesive but not under ceramic disc). May need to hold therapy until a grade 1 Grade 3: treatment interruption and possible dermatology consult
Infections manifested by discharge, pustules, erythema, or crusting	Folliculitis is an infection that may occur from array changing and shaving Infections can occur from the occlusive nature of the array adhesive Always reassess skin every 2 weeks or sooner if needed Grade 1: culture and treat with topical prescription-grade antibiotic ointment Grade 2: culture and treat with oral antibiotics. Avoid direct contact of affected area. May need to hold therapy until a grade 1 Grade 3: culture and treat with oral antibiotics; possible dermatology consult. May need to hold therapy until a grade 1
Ulcerations - epidermis and dermis are destroyed	Discharge indicates infection. Crusts with healing Always reassess skin every 2 weeks or sooner if needed Grade 1: treat with topical prescription-grade antibiotic ointment Grade 2: treat with topical and oral antibiotics. Avoid direct contact of affected area. May need to hold therapy until a grade 1 Grade 3: treatment interruption and dermatology consult

Abbreviation: AEs, adverse events.
Adapted and reprinted with permission from Lacouture et al.[24]

0.75 inches) from their previous position will vary contact sites and reduce the risk of skin irritation. The ceramic discs leave a slight indentation, allowing caregivers to see where previous arrays were placed and to avoid the same position. Caregivers should reference the patients individualized array layout map that is provided at initiation of treatment.

Even with the most stringent scalp preparation skin irritation can still occur. Skin can become dry, flaky, and itchy from previous radiation exposure, environmental changes, medications, and

array changes. Chemical irritation from hydrogel, moisture, and/or alcohol can cause irritant contact dermatitis; however, an allergic contact dermatitis may also occur from an allergy to tape and/or hydrogel.[24] It may be helpful for patients to send pictures of skin changes to the health care team to treat irritation appropriately.

Mild to moderate contact dermatitis can be treated with high-potency topical steroids, such as clobetasol, with each array change until the reaction resolves.[24] Mild skin irritation or flaky, dry skin can be treated topically with creams or mild, fragrance-free shampoo and conditioner. Topical antibiotics, such as mupirocin, may be used on open sores or any area of mild skin breakdown.[24] If possible, patients should be instructed to avoid direct contact of discs and adhesive tape to the reaction site. Patients with skin breakdown or an open sore should be instructed to cut a hole in the adhesive tape around the affected area, which will allow skin to breathe, ability to apply topical antibiotic more frequently, and promote faster healing.[24] Applying nonstick gauze to the area of concern and then placing the adhesive over that may also aid in preventing further skin breakdown. If a skin reaction becomes severe, the patient may need a dermatology referral or interruption of treatment until the symptoms resolve.[26]

Quality of Life

Managing QoL when diagnosed with a GBM is a common concern in the brain tumor patient population. Learning to cope with physical, mental, cognitive, and treatment changes along their journey affects the patient's overall QoL. Health-related QoL (HRQoL) was measured as a predefined secondary endpoint in the EF-14 pivotal phase 3 study, which was measured with the European Organisation for Research and Treatment Quality of Life Questionnaire-C30 (EORTC-C30) with the brain symptom-20 (BN20) supplement. These questionnaires were initiated before randomization for a baseline then followed every 3 months for up to 12 months. There were nine predefined scales and items determined to be significant to the brain tumor population. A detailed QoL analysis of the EF-14 trial showed that the addition of TTFields to TMZ did not negatively impact QoL. Itchy skin under the transducer arrays was the only exception.[25] Patients treated with TTFields and TMZ versus TMZ alone reported stable or improved in the following categories: global health status (53% *v* 38%), physical functioning (54% *v* 38%), as well as leg weakness (59% *v* 42%) and pain (56.8% *v* 35%). Because of their longer PFS, patients reported a better QoL for a longer period of time when treated with TTFields and TMZ versus TMZ alone (Table 3).[27]

Implications for Oncology Nurses

The diagnosis of GBM transforms the life of the patient and additionally impacts the life of their family and friends. Patients and their caregivers put their trust into the medical and nursing team to give them the best possible options to battle this disease. Nurses play a pivotal role in gathering the right information from the patient and assisting them with deciding on the best treatment option.

TABLE 3.
Secondary Analysis of TTFields: Stable or Improved HRQoL during Progression-Free Time

Health-related Life Domain	TTFields plus TMZ (%)	TMZ Alone (%)	*P* value
Stable improved from baseline (%)			
Global health status	53.5	37.6	.001
Physical functioning	54.0	38.0	.24
Cognitive functioning	50.4	38.7	.02
Role functioning	47.9	41.1	.17
Social functioning	48.2	40.8	.14
Emotional functioning	54.6	43.7	.03
Pain	56.8	35.9	<.001
Itchy skin	42.4	46.7	.0056
Weakness of legs	58.7	42.0	.001

Data from Taphoorn et al.[27]

Until recently, standard-of-care treatment for GBM utilized only radiation therapy and chemotherapy. FDA approval of TTFields now allows an additional treatment possibility, especially for patients unable to tolerate chemotherapy. It is important for the nurse to understand the TTFields mechanism of action, the implications for use, and the Optune device components to better educate the patient about this standard-of-care option. TTFields are indicated for use in the adult population, 22 years of age or older, with supratentorial lesions. Patients sensitive to hydrogel or adhesive tape may not be able to tolerate the array placement because of allergic reaction. TTFields were not studied in patients with active implanted medical devices and is not recommended by Novocure. A study by Kew and colleagues[28] examined the use of TTFields in individuals with shunts, pacemakers, or defibrillators to evaluate safety. Although a small study, there were no unexpected safety issues that would prevent patients from the use of TTFields concurrently with implanted devices.[28] Future studies evaluating the stability of programmable shunt valves and the simultaneous use of TTFields are currently underway.[29]

Even with the positive outcome data and the allocation of standard-of-care status, there are still challenges that concern patients when incorporating TTFields into their treatment plan. Having to shave their head a couple of times a week, routinely wearing arrays, and carrying around the operating system can be perceived as unwarranted tasks. Patients are challenged with physical and cognitive deficits and are reluctant to wear the device that advertises their glioma diagnosis. However, evidence has shown that QoL was maintained while wearing the device.[27] Thus, educating patients about the maintenance of QoL upfront is a positive way to initiate conversation. This conversation may occur multiple times during the early phases of care.

Speaking to patients about the outcome data is also important. Maximal tumor debulking is the best surgical option for patients with glioma, but often the tumor location may not allow for a total resection. Final subgroup analysis of the EF-14 trial data revealed that even patients that had only a surgical biopsy or partial resection with standard of care had improved median survival when they wore the device.[13]

Assessing the patient's performance status and psychological and cognitive function are all determining factors in the operation and use of the device. Incorporating the device into one's daily lifestyle requires a commitment by the patient and caregiver. Knowing the social aspects and family dynamics will assist in determining the support systems at home and will help incorporate the device into the patient's daily routine. The components and operating system of the device are easy to learn and are usually taught within a short period of time; this includes managing and caring for the components of the system as well as managing the device alarms.[23]

To enhance the patient's knowledge, the oncology nurse can utilize various resources to assist patients, caregivers, and health care providers address device challenges. There is 24/7 support though Novocure's nCompass Program for patients and caregivers who need assistance with non-medical management of the device. A company-provided, in-home Device Support Specialist is available for initial training and can identify and rectify technical challenges for the patient. However, it is the health care team's responsibility to manage medical symptoms related to the device.[29] Nurses can refer patients to a program that provides support to patients and caregivers through one-on-one interaction with current patients and caregivers utilizing the device. For patients just learning about this form of treatment there are brochures and videos available to health care providers. Incorporating these resources is vital to providing accurate information to everyone involved in the treatment decision and the optimal care of the patient.

To get the most benefit from the device a patient must be able and willing to wear the device a minimum of 18 hours a day, or 75% of the time. If patients are required to withhold treatment because of severe adverse reactions, the patient's compliance will decrease, therefore diminishing the effects of treatment. It is important to note that admitted patients can continue to wear the device without any precautions. Additionally, wearing TTFields does not pose threat to those in close proximity to the patient.[23] The device will need to be removed for an MRI, but may be reapplied after MRI evaluation.

The nurse's role in encouraging patient adherence is key to the success of treatment based on recent compliance data indicating that patients did significantly better when wearing the device more than 18 hours day. It is important to facilitate compliance of the device, just as patients must adhere to medications appropriately.

Providers are given a compliance report (Fig. 5) each month, which allows open communication between patient and health care provider regarding usage of device. The report can determine what is and is not working and can also provide a method for establishing patient incentives and goals. Patients should be aware there is a learning curve for the first few months wearing TTFields and compliance may not be at the level they expected. Nurses can help improve patient compliance with open dialogue about managing expectations, minimizing time off the device, and determining how to best incorporate the device into their normal daily routine. It is important to educate patients that the device can be worn during certain activities, such as jogging, golf, or working around the home. However, they must remember to properly turn the device back on after showering or using the restroom.[26] Patient adherence may also increase by emphasizing that therapy is continuously being delivered only while the device is turned on, unlike chemotherapy or other pharmaceutical treatment where efficacy is decreased as the drug is metabolized. Finally, it is important to note that both patient and caregiver (s) must be committed to this type of treatment in order for it to be successful. Without commitment of both parties, compliance rates decrease and can lead to a decreased QoL of patient and caregiver because of the perceived burden of the device. Making patients aware of improved survival statistics related to compliance may motivate increased usage of the device.

As the number of patients utilizing TTFields increases, both in newly diagnosed and recurrent settings, additional trials should be considered to address skin care management. Many intrinsic and extrinsic elements may influence injury to the skin. Skin irritation and itchy skin are the most prevalent side effects when wearing the device, and assessing outside factors should be taken into consideration before array application. The elderly population have a loss of skin elasticity, subcutaneous tissue, and epidermal moisture, which may put patients at a higher risk for skin injury. Extrinsically, radiation treatment and the use of certain medications may result in irritation and thinning of the skin, which may affect skin integrity when applying and reapplying the device. Along with proper skin care protocols, developing the use of a skin assessment tool such as the Neonatal skin risk assessment scale[30] may be advantageous when

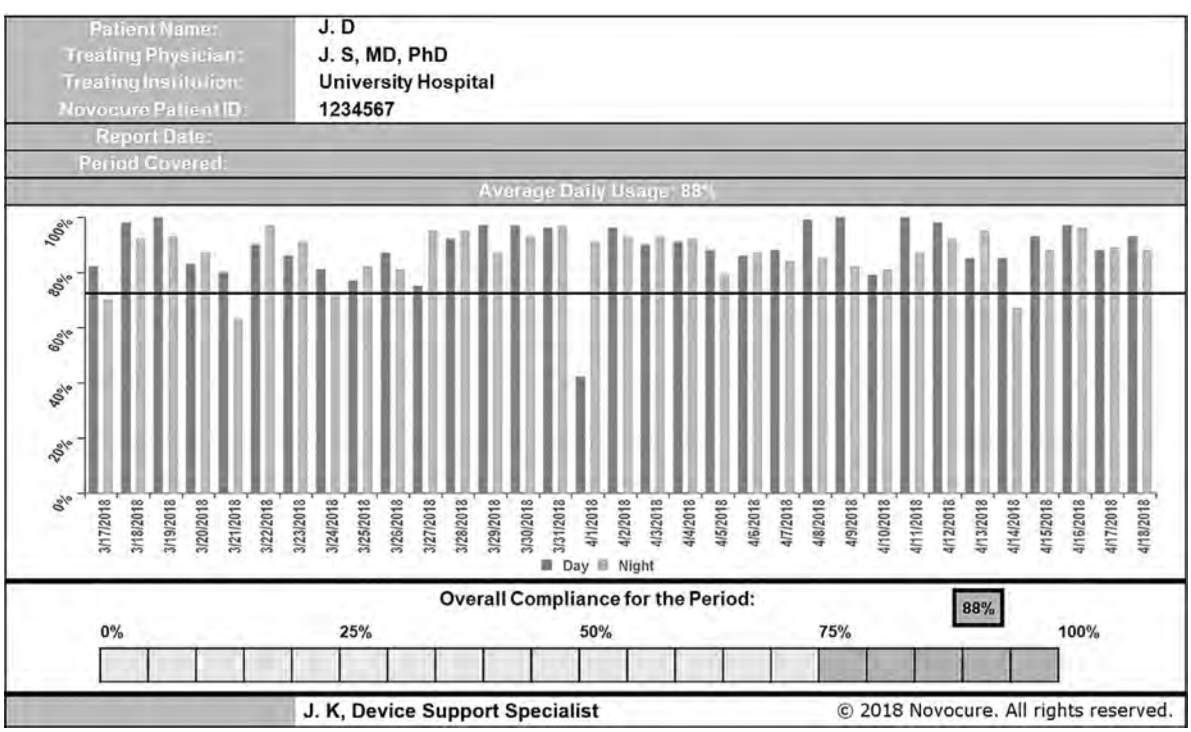

FIGURE 5. Example of a compliance report. (Reprint with permission of Novocure).

assessing the skin prior to array placement. This scale assesses general physical condition, mental state, mobility, activity, and moisture, which could benefit the patient.[30,31]

Products such as antiperspirants, moisturizing creams, and skin barriers may play a role in relieving skin irritation from TTFields. However, it has been shown that not all products are compatible with TTFields because they may increase electrical impedance that may cause increased temperatures under the arrays.[32]

Ongoing research continues to evolve with TTFields and GBM. Current trials are evaluating the synergistic effect of TTFields in combination with radiation therapy or immunotherapy and the direct response it has on tumor control.[23] Various trials continue to emerge regarding the use of TTFields in children as well as other solid tumors. Ongoing TTField trials are also being studied in brain metastases, lung cancers, ovarian cancer, mesothelioma, and pancreatic cancer.[23]

Conclusion

Although the prognosis of GBM remains poor, improvements are emerging. Treatment options remain limited for patients with a GBM, but the addition of TTFields has shown significant improvement in overall and PFS. As the field continues to grow it is imperative for nurses to continue research on the new technologies, treatments, and advances that emerge in the field. Patients and their families seek information regarding the disease process and its treatments. Working within their scope of practice, nurses are uniquely positioned to deliver education and support to patients and families through excellent nursing care grounded on an evidence-based approach. It is critical with this and other new and innovative therapies that oncology nurses be informed of the data to educate health care providers, patients, and their caregivers when deciding on evidence-based treatment options that impact OS and QoL.

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Tumor Treating Fields Technology: Alternating Electric Field Therapy for the Treatment of Solid Tumors

Laura Benson

Objective: *To provide an overview of Tumor Treating Fields (TTFields) and the Optune device in the treatment of glioblastoma multiforme as well as discuss the evolution of TTFields technology for the treatment of different tumor types.*

Data Sources: *Peer reviewed publications, proceedings, and Internet-based resources.*

Conclusion: *TTFields represent a unique technological modality for the effective treatment of glioblastoma multiforme and potentially other solid tumors. Oncology nurses are situated to play important roles as educators and advocates for patients and caregivers on the adherent use and management of this new and evolving treatment technology.*

Implications for Nursing Practice: *The increasing use of TTFields in cancer treatment draws attention to the expanding role for oncology nurses in the administration of this unique therapy. As an educator and advocate, the oncology nurse guides the cancer patient and caregiver through understanding the mechanism of action, initiation of TTFields treatment, and adjusting to the daily challenges of treatment administration, management of side effects, and optimizing compliance to treatment adherence to maximize treatment outcomes.*

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Key Words: *tumor treating fields, TTFields, glioblastoma, tumor treatment.*

Tumor treating fields (TTFields) are a distinct technological modality for the treatment of solid tumors. TTFields therapy is non-invasive, and the therapeutic effect is achieved through the regional delivery of low-intensity, intermediate frequency-specific (100 to 300 kHz), alternating electric fields to the site of a tumor in the body.[1-3] TTFields are generated between opposing ceramic transducers strategically placed directly on the skin on opposite sides to create alternating electric fields through targeted tumor regions. TTFields act with a high degree of specificity on rapidly replicating cancer cells (Fig. 1), exerting disruptive forces on mitotic spindle formation, resulting in mitotic arrest and cancer cell death. TTFields also exert forces on intracellular organelles and macromolecules during cytokinesis, causing abnormal chromosomal segregation and multinucleation, thus further affecting the replication of daughter cells. Components of rapidly dividing cancer cells that carry a charge are attracted strongly to the alternating electric fields rather than to the weakly charged intracellular components and forces driving cell division. This leads to incomplete mitosis and apoptosis. Quiescent and non-dividing cells are not affected by TTFields.[4-6] The mechanism of action of TTFields is an area of intense research exploring many concepts, such as the role of immunology, migration, and autophagy.[7,8] The data from these studies demonstrate how TTFields therapy targets cancer cells with electric fields tuned to a specific frequency optimized for suppression of cancer cells in different types of solid tumors. Figure 2 shows micrographic images for cells from different tumor types and the optimal frequency for TTFields to suppress proliferation of cells from specific cancer types. Unlike systemic treatment modalities (eg, chemotherapy), TTFields are only active while the alternating electric fields are applied, underscoring the need for vigilant

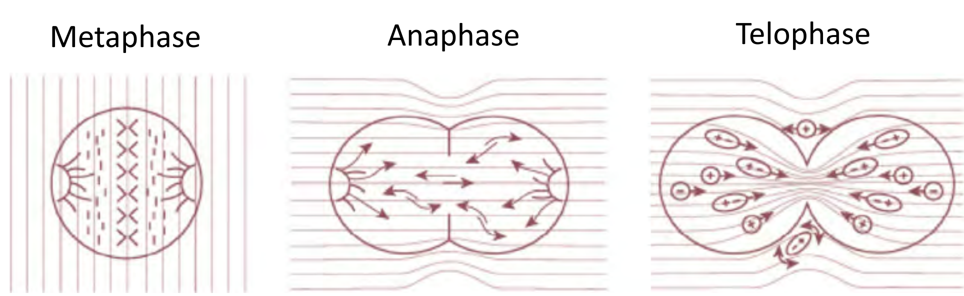

FIGURE 1. TTFields mechanism of action: TTFields act on rapidly dividing cancer cells by disrupting mitotic spindle assembly during metaphase/anaphase. TTFields also produce nonuniform electric fields within cancer cells affecting intracellular organelles and macromolecules during cytokinesis and causing abnormal chromosomal segregation and multinucleation (telophase) effecting further replication of daughter cells.

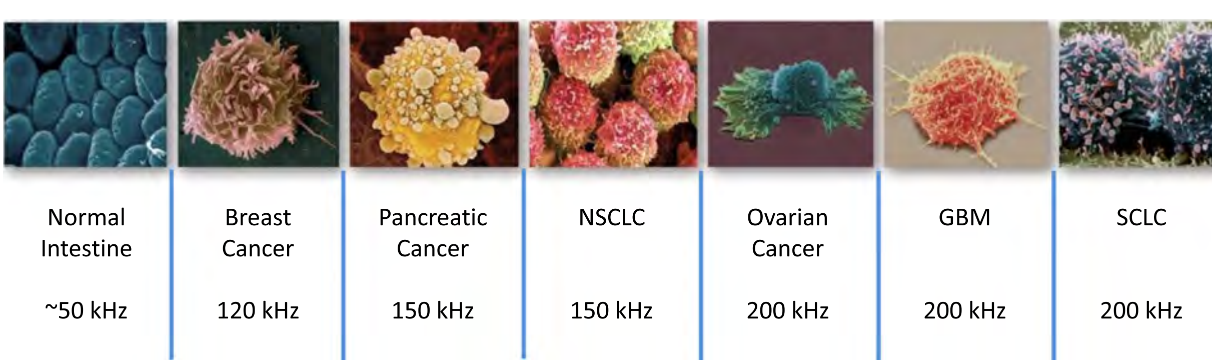

FIGURE 2. TTFields effects on cancer cells are frequency specific.

adherence to TTFields treatment (≥18 hours per day is the recommended duration of treatment of glioblastoma multiforme [GBM] for maximal clinical benefit). TTFields are a wearable, portable medical device that are administered by the patient at home. As a regional targeted therapy, with no systemic half-life, TTFields treatment is not associated with systemic adverse effects and therapy can be stopped immediately should a patient experience any issues with treatment. The use of TTFields is unique among other devices in medicine in that the administration of TTFields with the device has a defined therapeutic effect with beneficial clinical outcomes rather than playing a secondary supportive role.

Clinical Development of TTFields for GBM

The initial evaluation of TTFields therapy in clinical trials was for the treatment of recurrent GBM in the supratentorial region with TTFields applied at a frequency of 200 kHz. GBM tumors are the most common and aggressive brain tumor in adults with a rapid onset of symptoms and a poor prognosis for survival after primary treatment.[9,10] Preliminary pilot studies in recurrent[1] and newly diagnosed GBM[11] demonstrated the viability of TTFields treatment for GBM with a good tolerability profile. Table 1 summarizes the

TABLE 1.
Summary of TTFIelds studies of the treatment of GBM

Study	Design	Highlighted outcomes
Recurrent GBM		
Kirson et al[1]	Phase I – pilot clinical trial – 10 patients with recurrent GBM	Median time to disease progression was 26.1 weeks and median OS was 62.2 weeks. No device-related serious adverse events were reported over 70 months of cumulative treatment in all patients
Stupp et al[3]	Open-label, phase III trial of chemotherapy-free treatment of NovoTTF (20–24 h/day) vs. active chemotherapy. Patients randomized to TTFields alone (n = 120) or active chemotherapy control (n = 117).	Median survival was 6.6 vs. 6.0 months (P = .27), 1-year survival rate was 20% and 20%, PFS rate at 6 months was 21.4% and 15.1% (P = .13), respectively, in TTFields and active control patients. The TTFields-related adverse events were mild (14%) to moderate (2%) skin rash beneath the transducer arrays
Newly Diagnosed GBM		
Kirson et al[11]	Pilot clinical trial in recurrent and newly diagnosed GBM patients	In newly diagnosed GBM patients, combining TTFields with temozolomide treatment led to a PFS of 155 weeks and OS of 39 + months
Stupp et al[12]	Interim analysis of an open-label, randomized, phase III trial of TTFields in combination with temozolomide for treatment of glioblastoma after initial treatment with chemoradiation	The interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 randomized to temozolomide alone, and was conducted at a median follow-up of 38 months. Median PFS was 7.1 months in the TTFields plus temozolomide group and 4.0 months in the temozolomide-alone group (P = .001). Median OS in the per-protocol population was 20.5 months in the TTFields plus temozolomide group and 15.6 months in the temozolomide-alone group (n = 84) (P = .004). TTFields plus temozolomide was not associated with any significant increase in systemic toxic effects compared with temozolomide therapy alone
Stupp et al[13]	Full patient analysis set of open-label, randomized phase III trial of TTFields in combination with temozolomide for treatment of glioblastoma after initial treatment with chemoradiation	A total of 695 patients were randomized; the median PFS is 6.7 months for patients in the TTFields plus temozolomide group vs. 4.0 months in the temozolomide-alone group. Median overall survival from randomization is 20.9 months vs. 16 months for the TTFields plus temozolomide and temozolomide alone, respectively (P = .00006).

Abbreviations: GBM, glioblastoma multiforme; OS, overall survival; PFS, progression-free survival.

outcomes of studies on TTFields therapy for the treatment of GBM.

The large EF-11 phase III multicenter clinical trial compared the efficacy and safety of TTFields (200 kHz) alone for the treatment of patients with recurrent GBM to patients treated with standard-of-care chemotherapy.[3] The median survival for the TTFields-treated patients was comparable with the standard of care (6.6 months vs. 6 months) and the 1-year survival rate was 20% for both treatment arms. Progression-free survival (PFS) at 6 months was 21% for TTFields compared with 15% for the standard-of-care treatment group. TTFields therapy was found to be as effective as chemotherapy with fewer side effects. Patients in the TTFields monotherapy treatment arm also reported better quality of life with improved cognitive and emotional functioning.[3] Based on the results of this study, TTFields therapy was approved by the US Food and Drug Administration (FDA) in 2011 for use in adults who have recurrent GBM after receiving chemotherapy and whose disease is refractory to surgical and radiation treatment options.

TTFields for Newly Diagnosed GBM

Preclinical data demonstrated that the combined administration of temozolomide (TMZ) and TTFields to human glioma cells in vitro had an additive cytotoxic effect,[1] suggesting the addition of TTFields to TMZ (the standard maintenance therapy for GBM following surgical resection and chemoradiotherapy) would potentially benefit newly diagnosed GBM patients. Based on this hypothesis, a phase III study was initiated in patients with newly diagnosed GBM in the supratentorial region who had completed concomitant standard-of-care chemoradiotherapy. Patients were randomly assigned (2:1) to receive either TMZ combined with TTFields (200 kHz) or TMZ alone. Based on a prespecified interim analysis of 315 patients demonstrating positive outcome, the trial was terminated early at recommendation of the independent data and safety monitoring committee and the FDA. Patients in the TMZ-alone arm were allowed to cross over to the TMZ-plus-TTFields group. Two thirds of patients in the combined TTFields and TMZ treatment group continued with TTFields treatment after the first tumor progression.[12] The interim analysis demonstrated that adding TTFields to maintenance TMZ significantly prolonged PFS (7.1 months vs. 4.0 months (hazard ratio, 0.62 [98.7%CI, 0.43–0.89]; $P = .001$) and overall survival (OS; 20.5 months vs. 15.6 months) (hazard ratio, 0.64 [99.4%CI, 0.42–0.98]; $P = .004$).[12] Based on these results, the FDA approved TTFields for use in combination with TMZ for the maintenance treatment of adult patients with newly diagnosed GBM. Recent results from the analysis of the 5-year full data set (695 patients) confirm the improvements in PFS and OS seen in the interim analysis.[13] The 2- and 5-year survival rates were 43% versus 31% ($P = .0008$) and 13% versus 5% ($P = .0037$) for TTFields plus TMZ versus the TMZ treatment alone group, respectively. Significant improvement in OS was seen for all patient subgroups. TTFields treatment compliance was the only predictor of outcome, with patients who achieved more than 18 hours/day (monthly average) living significantly longer than patients treated for <18 hours/day.[13] The National Comprehensive Cancer Network guidelines recommend TTFields as a standard treatment category 2A option for newly diagnosed GBM in patients with good functional status.[14]

The objectives of this review are to highlight the technology on which TTFields therapy is based, the impact of its use in the treatment of GBM, as well as discuss the potential evolution of TTFields' technology for the treatment of other tumor types.

Optune: Patient-Operated, Home-Use TTFields Delivery System

The first-generation Optune device (Novocure Inc., Portsmouth, NH; formerly known as the NovoTTF-100A System) was designed for TTFields treatment in the home with minimal impact on activities of daily living. A lighter and more compact second-generation device (NovoTTF200A) was approved for use by the FDA in 2016. Table 2 compares both the first- and second-generation devices. Optune is a CE (Conformité Européenne) marked device approved for use in the European Union, Switzerland, Australia, Israel, and Japan for GBM. The second-generation system takes advantage of improvements in electronic components, circuit boards, and digital signaling technology.

The NovoTTF 200A system[15] is comprised of two primary components: the electric field generator (preset to 200 kHz) and insulated transducer arrays. The device treatment kit includes a plug-in power supply, portable battery, battery rack, battery charger, connecting cables, and carrying case (see

TABLE 2.
First- and second-generation (right) Optune systems for GBM

	First-generation Optune System	Second-generation Optune
		
Total weight (Device and battery)	6 lbs	2.7 lbs
TTFields generator (The device)	2 lbs	1.5 lbs
Battery Weight	4 lbs	1.2 lbs
Size	Device: 8.3 x 8.3 x 1.75 in Battery: 8.25 x 8.25 x 1.1 in	Device with incorporated battery: 7.1 x 2.3 x 7.6 in
Features	Portability	Easy-grip texture allows for better handling

photos comparing the first- and second-generation systems in Table 2). Studies in vitro show that the response of cancer cells to TTFields is directionally dependent with higher inhibitory rates of cell replication in cells dividing perpendicular to the electric field direction.[4] Therefore, the placement of the transducer arrays are designed to maximize the clinical effect of TTFields treatment by utilizing two pairs of transducer arrays that are applied directly to the skin to produce two perpendicular electric fields at a specific frequency for the tumor type. Each pair of transducer arrays creates an electric field that is alternating between positive and negative polarity 200,000 times per second (200 kHz) for GBM, and at every second the fields switch between the two pairs of arrays. This is referred to as a duty cycle.

Each transducer array used to treat GBM lesions within the cranium is composed of nine insulated biocompatible ceramic discs connected to a flexible circuit board and in turn to the electric field generator. The field generator is operated at a frequency of 200 kHz when treating GBM. The discs are arranged in a hypoallergenic adhesive bandage to hold them securely in the proper orientation and are attached directly to the shaved bare skin with an intermediary layer of conductive hydrogel.[16] There are reports of patients experiencing warmth with the transducer arrays in place and the field generator turned on; for safety, each transducer array has eight temperature sensors that will sound an alarm and shut the device off should the temperature of the array exceed 41°C, which is below the temperature for thermal injury.[16] Integrated device system sensors will sound an alarm in the event of operational and safety issues, such as low battery, loose connectors, overheating of the TTFields generator or the transducer arrays, or poor contact between the transducer and skin surface.

The second-generation TTFields device (including the battery) is smaller and lighter with an overall weight of 2.7 lbs (Table 2) and is designed to be carried more comfortably with improved usability for the patient compared with the first-generation device. The second-generation device was made lighter and smaller using unique digital signal generation technology. Additional technical improvements include: a battery indicator that displays power and alerts patients when to change the battery; a light-detecting sensor that automatically dims the device and charger in darker environments; and features "No-Stop Swap" batteries that allows patients to change batteries or power source without turning off delivery of TTFields treatment. Patient feedback regarding the second-generation device highlights the benefits of

quieter operation and portability. Patients experienced fewer alarms and showed greater adherence using the second-generation device that was maintained or improved in most cases compared with the adherence rates observed with the original device.[17]

Adherence with TTFields treatment is critical for clinical benefit. TTFields are a loco-regional therapy, active only while the electric fields are generated between the transducer arrays and distributed to the site of the tumor. Therefore, the clinical effect is only active when the arrays are in place and the TTField generator is on. In a study of post-marketing surveillance, patients with high daily adherence, defined as ≥75% (≥18 hours/day) of average daily adherence with TTFields therapy had a significantly longer OS when compared with patients who fell below the 75% therapy duration.[18] A post-hoc analysis of patient data from a pilot study and a phase III trial also demonstrated improved survival with adherence to longer daily duration of therapy (≥18 hours/day)[19,20] and treatment compliance was the only predictor for long-term patient survival in the full analysis of the EF-14 trial patient data set.[21]

As monotherapy for recurrent GBM, TTFields in the EF11 study was associated with improvement in patient-reported assessments of cognitive and social functioning when compared with standard-of-care chemotherapy and symptom scale analysis showed an increase in treatment-associated toxicity directly related to the chemotherapy regimen, such as pain and fatigue that was not reported for patients in the TTFields treatment group,[3,22] suggesting quality of life benefits with TTFields treatment.

In addition to adherence, optimal placement of the transducer arrays may account for improved clinical outcomes. State-of-the-art technological research using modeling and simulations have demonstrated that changing the transducer array placement on the skin to address specific tumor locations results in substantial increases in the induced field intensity within the tumor (Fig. 3), supporting individualized treatment planning for GBM patients.[23] The NovoTAL System is an algorithmic software program validated by a user study group that optimizes transducer array layouts for an individual GBM patient based on head size and tumor location using measurements obtained from magnetic resonance imaging (MRI) data.[24] The algorithm will derive the optimal paired transducer array configuration to deliver the highest intensi-

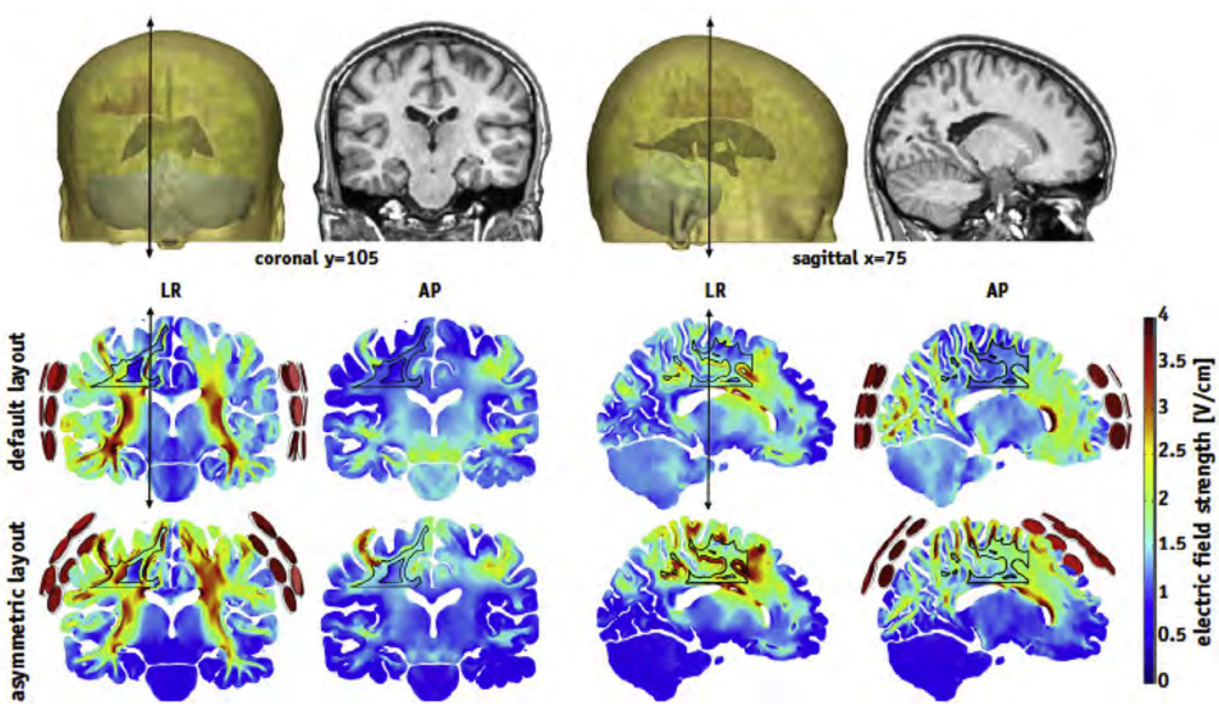

FIGURE 3. Transducer array placement influences TTFields intensity distribution. Simulation studies demonstrate the effect of array placement on electric field intensities across brain tissue. The objectives of such studies are to ensure optimal TTFields intensity at the site of the tumor.[23]

ty of TTFields to the site of a tumor (Fig. 4). The NovoTAL System was approved by the FDA in 2013.[25] The Optune device uses preset treatment levels for frequency (200 kHz for GBM) and a minimal field intensity of 0.7 V/cm across the brain tissue and site of the tumor.[16,26] Follow-up MRI imaging is regularly performed after TTFields therapy is started to track treatment effect and rule out recurrence.[19] In patients with recurrent GBM, 44% of GBM tumors that respond to TTFields treatment initially showed growth before shrinking in size after a median of 4 months with continuous TTFields therapy.[19] A series of case studies presented by Turner et al[27] show evidence for "out-of-field" tumor recurrence potentially because of suboptimal field intensity at the margins of the resected tumor bed. The observations imply that "remapping" the transducer array placement based on a change in follow-up MRI, may be an effective strategy to pre-emptively target tumor recurrence.

There are a few important contraindications and warnings associated with using the Optune system for the indicated treatment of either recurrent or newly diagnosed adults with GBM. The device should not be used in patients with active implanted medical devices (ie, deep brain stimulators, vagus nerve stimulators, pacemakers, or defibrillators), skull defects, or bullet fragments.[15] In the United States the FDA requires that the device must be prescribed by a health care provider who has completed certification training provided by Novocure.[15] Optune is classified as durable medical equipment and is typically covered under a patient's medical benefit with commercial insurance companies. Optune is covered by most commercial insurance companies under published coverage policy or through case-by-case review.

Patient and Caregiver Education to Optimize TTFields Delivery

A GBM patient's social, cognitive, and physical statuses all play a role in determining whether the patient is a good candidate for TTFields therapy. Patients with physical and cognitive impairment and lacking good daily support are not likely to achieve the recommended adherence goals that are optimal for clinical benefit. Ideally, a patient should have at least one support person who can assist the patient if needed. This is to assist with device alarms, adverse events, and help with removing and

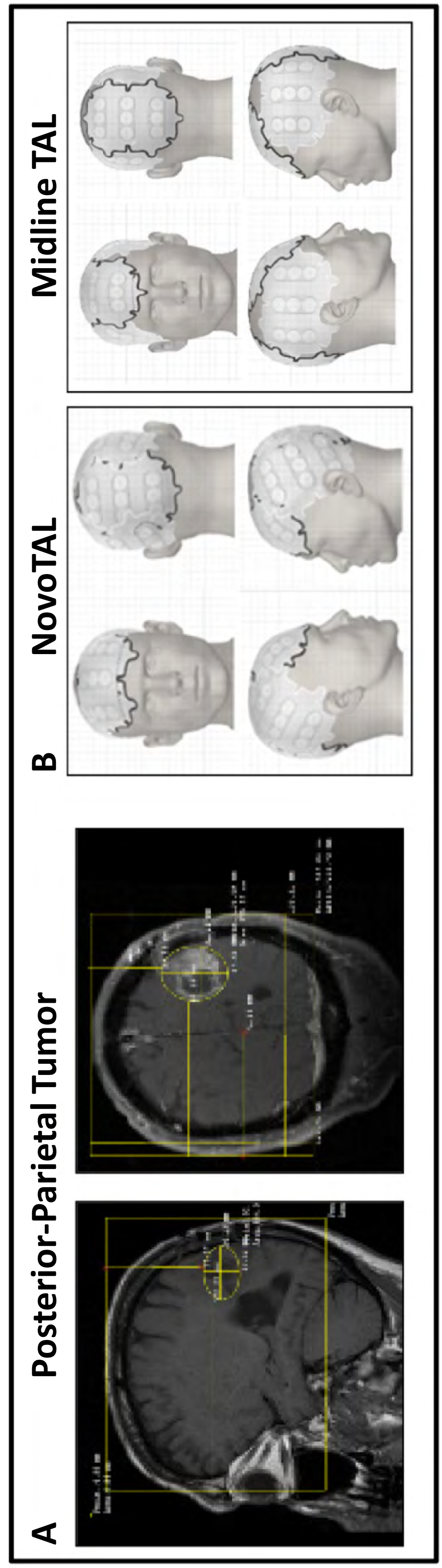

FIGURE 4. NovoTAL treatment planning. (A) Representative NovoTAL treatment planning performed on MRI sagittal and axial T1 post-contrast sequences of a posterior-parietal tumor. (B) Corresponding array layout generated using the NovoTAL System (left) and symmetric midline array configuration for the same tumor (right).[24]

accurately replacing the arrays as part of the normal treatment with TTFields.[28]

Patient and caregiver education are an essential part of TTFields treatment. Each should have a basic understanding of the mechanism of action, the components of the Optune system, how they work, and the importance of meeting treatment adherence goals.[17,29] Patients and caregivers are provided with training in advance of starting therapy with TTFields. This training includes instructions in caring for and maintaining the system components, managing system alarms, and how to prevent and manage skin irritation. Throughout training and follow-up, the importance of adherence to therapy is emphasized.

In general, patients are instructed to replace the transducer arrays at least every 4 days,[28] to reshave the scalp, and reapply new transducer arrays. Some patients may require more frequent array changing and reshaving. Used transducers and other system parts are returned for proper disposal. The time period for array replacement depends on individual hair growth, rates of sweating, activity level, and weather.[29] Both the first- and second-generation devices are portable so that patients can participate in activities of daily living with minimal inconvenience (Fig. 5). The redesigned second-generation device is currently used by patients receiving treatment for GBM. The first-generation device is currently used in ongoing investigations in other tumor types delivering therapy at different frequencies. It is also important to note that TTFields therapy poses no danger to anyone in close proximity to the patient. The health care team including nurses supporting the patient and caregiver can help develop strategies to minimize the intrusion of TTFields therapy and the device on daily activities. Strategies include selecting wigs and hats if the patient wants to disguise the transducer arrays when out in public. Because restrictive or tightly woven wigs or hats will trap heat and effect device operation, selecting scarves, loosely woven or ventilated wigs appropriately sized for the patient will dissipate heat more effectively while covering the arrays.[29] The cables connecting the power supply and field generator to the transducer array can be arranged under selected layers of clothing to make them less obvious and intrusive.

The device is designed to assist the patient, caregiver, and health care team achieve optimal device-wear time goals. A patient-specific compliance report, compiling daily use times is generated monthly to track the percentage of active TTFields delivered over a 24-hour period. The reports provide tangible evidence for review with the patient and caregiver to help identify issues with adherence so

FIGURE 5. Portability of the Optune device allows patients to participate in activities of daily living. (Photo with permission from the patient.).

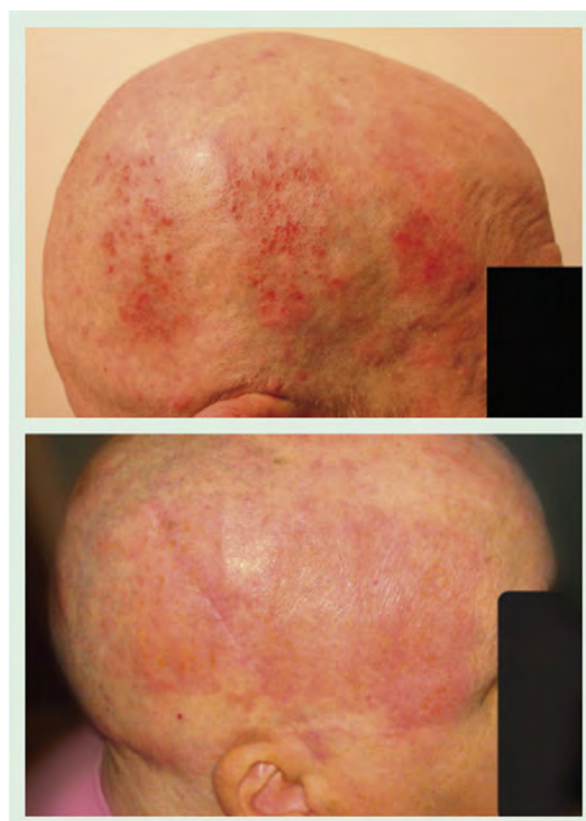

FIGURE 6. Examples of contact dermatitis reactions related to long-term TTFields treatment. Erythema from scalp irritation associated caused by adhesive or hydrogel is shown in the upper panel. The lower panel shows an irritant reaction with erythema associated with the hydrogel between the transducer arrays and the scalp.[16]

that strategies can be adopted to improve treatment duration and potentially improve clinical response.[29] Novocure provides device support specialists trained to assist patients and caregivers with the daily operation of the system.[28] The patient's device support specialist provides comprehensive training and counseling to the patient on the operation of the Optune device and guidance on specific placement of the transducer arrays. The device support specialist also downloads the monthly adherence report, which is provided to the health care team. This is a valuable tool to monitor the patient time on therapy, to reinforce teaching, and to provide coaching on an ongoing basis. The monthly report provides a mechanism to assist with achieving optimal treatment adherence goals.[28] The entire health care team utilizes the data available from the Optune system, along with the full spectrum of clinical data, including MRI imaging, to make the required clinical decisions to optimize treatment outcomes for each patient.

The most common adverse events related to the use of either the first- or second-generation device are scalp irritation and headache.[3,12] These events are usually mild to moderate in severity and occur below the transducer array and adhesive bandage. Dermatologic adverse events fall into the following categories: irritant contact dermatitis caused by sweat, hydrogel, and/or alcohol; allergic contact dermatitis from a delayed type hypersensitivity reaction to the array adhesive or hydrogel; mechanical erosions from cuts from shaving or removal of the arrays; ulcers caused by inhibited perfusion as a result of the arrays pressing on the skin; and bacterial skin infections.[16] Examples of contact dermatitis reaction-related TTFields treatment are shown in Figure 6. Adequate skin preparation is essential for effective contact between the array transducer and skin, and good scalp hygiene and array placement are critical components of maintaining long-term skin integrity.[28] Effective strategies for preventing and managing skin irritation are summarized in Table 3. Most dermatologic adverse events can be managed with topical treatments and slight adjustment of the transducer arrays to minimize skin irritation.[16] A treatment algorithm for managing dermatologic adverse events is shown in Figure 7.

TABLE 3.
Preventive strategies for dermatological adverse events related to Optune TTFields treatment[16,29]

Category	Guidelines for patient and caregiver
Shaving and preparation of the scalp	• An electric shaver is recommended, having a lower risk to cause cuts compared with a razor • Proper hand washing prior to preparing the scalp for array application • Take time shaving the scalp using gentle but firm circular motions • Ensure a close shave before applying the arrays • Cleaning the electric razor after every shave is important to lessen the risk of skin infection • Wash scalp with fragrance-free, mild shampoo (eg, baby shampoo); seborrheic dermatitis shampoo can also be used as it has antibacterial properties (eg, pyrithione zinc 2%, ciclopirox 1%, ketoconazole 2%) • Ensure scalp is completely dry before applying a new set of arrays
Use of isopropyl (70%) alcohol	• Use of first aid antiseptic rubbing alcohol (70% isopropyl alcohol) prior to array application is a necessary step to remove naturally occurring scalp oils, resulting in better adherence of the arrays to the scalp • After shaving and before placing the arrays, wipe the scalp with a gauze or cotton ball soaked in first aid antiseptic rubbing alcohol (70% isopropyl alcohol) • Avoid areas of skin irritation, as the first aid antiseptic rubbing alcohol (70% isopropyl alcohol) may further irritate the skin
Transducer array exchanges	• Change arrays on a regular basis (at least every 3–4 days) • When removing the arrays, avoid "pulling" on the skin; take approximately 60 sec to remove each array • Use of mineral (baby) oil on the edges of the array may make removal of the adhesive tape easier and less irritating to the skin • To remove leftover array adhesive, use gauze or a cotton ball soaked in mineral (baby) oil or pour oil into hands and gently rub scalp in areas of remaining adhesive • Pay close attention to the scalp at each array exchange, and notify the doctor or nurse if there are signs of skin irritation or open areas, to receive information on how to treat them; taking a picture of the affected areas on the scalp and sharing it with the doctor or nurse is advised

	Type of Dermatologic Adverse Event and Recommended Interventions			
Severity	Dermatitis	Erosions	Infections	Ulceration
Preventive	Patient and caregiver education; shifting of transducer arrays; regular (every three to four days) changing of the transducer arrays; close attention to the condition of the skin at time of array exchange and open communication with the healthcare team related to any erythema or irritation; hand washing prior to array exchange to minimize risk of infection; avoiding placement of ceramic discs immediately over screws, wires, or scars; proper ventilation when covering arrays (e.g., ventilated wigs or caps, lightweight scarves)			
For all grades: Advise patients not to place array discs directly over affected area(s) when exchanging arrays. Assess how often the patient is doing an array exchange. Reassess after two weeks (either by healthcare provider or patient self-report). If reaction worsens or does not improve, proceed to guidance for next grade.				
Grade 1	High-potency topical corticosteroid ointments (e.g., clobetasol)	Topical antibiotics (e.g., mupirocin or bacitracin ointment)	Culture, then treat with appropriate topical antibiotic.	Open areas require topical antibodies.
For grade 1: Reassess after two weeks (either by healthcare provider or patient self-report). If reaction worsens or does not improve, proceed to guidance for next grade.				
Grade 2	High-potency topical corticosteroid ointments and avoidance of direct contact of discs and adhesive tape with affected area(s)	Topical and oral antibiotics and avoidance of direct contact of discs and adhesive tape with affected area(s)	Culture, then treat with appropriate oral antibiotic; avoid direct contact of discs and adhesive tape with affected area(s).	Topical and oral antibiotics and avoidance of direct contact of discs and adhesive tape with affected area(s)
For grade 2: Reassess in two weeks. Consider resuming tumor-treating fields therapy once event has recovered to grade 1.				
Grade 3	Treatment interruption; consider dermatology consultation.	Treatment interruption; consider dermatology consultation.	Obtain skin culture; oral antibiotics; consider treatment interruption until grade 1; consider dermatology consultation.	Treatment interruption; consider dermatology consultation.

FIGURE 7. Treatment algorithm for dermatologic adverse events associated with the use of Optune therapy.[16]

Future Tumor Targets for TTFields

Preclinical studies demonstrate that the optimal anti-proliferative effect of TTFields on isolated cancer cells is dependent on the frequency of the electric fields that is specific to the source of the isolated tumor cells.[4,6,30,31] Therefore, in the clinical setting, TTFields administration is applied at 200 kHz for GBM, representing the frequency with the greatest reduction in glioma cell proliferation[1] and at a frequency of 150 kHz for non–small cell lung cancer cells in vitro.[6,30] TTFields treatment effect is also dose-dependent, where "dose" is equated with the peak-to-peak alternating electric field intensity, which has a minimal threshold value of 1 V/cm. Below this value there is little effect on cancer cell proliferation.[1,4,6,29] Clinical development is currently underway for brain metastases from lung cancers (150 kHz), non–small cell lung cancer (150 kHz), ovarian cancer (200 kHz), pancreatic cancer (150 kHz), and mesothelioma (150 kHz).[32,33] Details regarding these phase II/III studies are summarized in Table 4. Preclinical studies are ongoing in the following cancer types; breast, cervical, colorectal, gastric, hepatocellular, melanoma, renal, urinary transitional cell and small cell lung cancer.

Radiation therapy (RT) is integral in the standard of care for GBM and other tumor types and targeted immunotherapies are evolving as viable treatment options for a variety of cancers. Preclinical studies suggest that there are synergistic effects for the combination of TTFields with RT and immunotherapies. TTFields administered before RT exposure sensitize glioma cell lines to RT damage and increase antimitotic activity through inhibition of cell survival, cell cycle regulation, and DNA repair activity.[34,35] These results suggest that clin-

TABLE 4.
Ongoing TTFields clinical trials for cancer[33]

Tumor type	Study name	Full title	Registration number	TTFields frequency
Brain metastases secondary to NSCLC	COMET	A phase II randomized study of TTField therapy (150 kHz) versus supportive care in non-small cell lung cancer patients with 1–5 brain metastases following optimal standard local treatment	NCT01755624	150 kHz
Ovarian carcinoma	INNOVATE	An open label pilot study of the NovoTTF-100L(O) system (NovoTTF Therapy) (200 kHz) concomitant with weekly paclitaxel for recurrent ovarian carcinoma	NCT02244502	200 kHz
NSCLC	LUNAR	Pivotal, randomized, open-label study of tumor treating fields (TTFields) (150 kHz) in combination with PD-1 inhibitors or docetaxel, for second line treatment of non-small cell lung cancer (NSCLC)	NCT02973789	150 kHz
Brain metastases secondary to NSCLC	METIS	Pivotal, open-label, randomized study of radiosurgery with or without tumor treating fields (TTFields) (150 kHz) for 1–10 brain metastases from non-small cell lung cancer (NSCLC)	NCT02831959	150 kHz
Pancreatic adenocarcinoma	PANOVA	A phase II study of TTFields (150 kHz) concomitant with gemcitabine and TTFields concomitant with gemcitabine plus Nab-paclitaxel for front-line therapy of advanced pancreatic adenocarcinoma	NCT01971281	150 kHz
Mesothelioma	STELLAR	A phase II trial of pemetrexed and cisplatin or carboplatin in combination with TTFields (150 kHz) as first-line treatment in malignant pleural mesothelioma	NCT02397928	150 kHz

ical trials of TTFields in combination with RT should be considered because the combination may improve the clinical benefit of RT. Early evidence suggests that TTFields combined with an immune check point inhibitor (anti-PD-1) augments immunogenic cell death and that combining TTFields with cancer immunotherapies may enhance tumor control.[36] Ongoing research suggests that there are potential complementary or synergistic effects when TTFields are added to chemotherapies or immunotherapies. Localized, regional therapy with TTFields may provide tumor control in combination with therapies having synergistic mechanisms of action without dose-limiting toxicity or compounding any potential adverse effects associated with the systemic treatment. The FDA recently (May 2017) issued a humanitarian use device designation for TTFields for the treatment of pleural mesothelioma, potentially leading to a Humanitarian Device Exemption approval in the United States.

The evolving use of TTFields for tumors in different parts of the body creates technological challenges regarding the design and application of the transducer arrays that deliver therapeutic intensities of TTFields to the site of the tumor and optimize therapeutic outcomes for the patient.[37,38] Digital phantom models (Fig. 8) and simulation analysis demonstrate that effective field intensities can be administered to target tumors in the thorax and abdomen. Typically the number, size, and arrangement of the transducer arrays for tumor treatment in the thorax and abdomen are larger than those used for cranial placement in the treatment of GBM. These parameters along with transducer array placement and arrangement within an array are factors integrated into simulation studies to optimize TTFields delivery to new tumor types and other regions of the body.

Implications for Oncology Nursing Practice

The increasing investigational use of TTFields in cancer treatment and the use of the Optune system for the treatment of GBM draw attention to the expanding role for oncology nurses in the

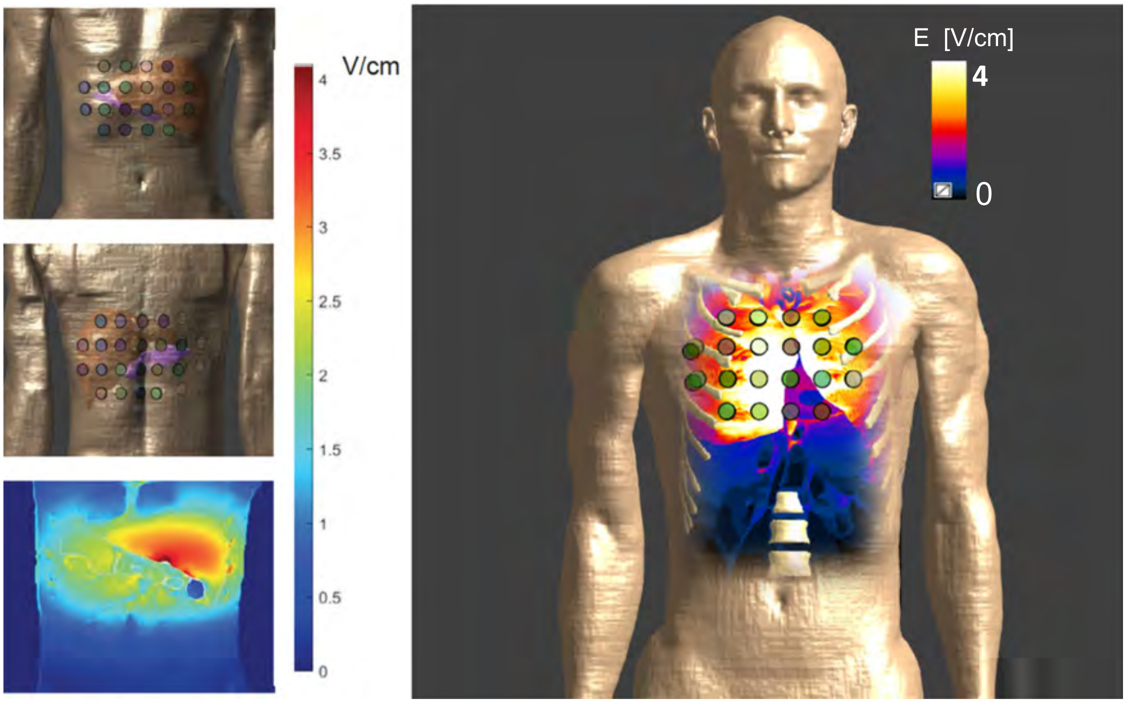

FIGURE 8. Calculated electric field intensity in the thorax when TTFields are applied to a male computational phantom model. Simulations demonstrate that optimized array placement can result in delivery of TTFields to treat tumors in the abdominal (right) and thoracic (left) cavities.[37,38]

administration of this emerging therapy. The use of TTFields represents a choice for a different and distinct additional therapeutic modality to consider when treating solid tumors. The best clinical outcomes for TTFields treatment are equated with good daily patient adherence (≥18 hours/day). Oncology nurses will play an important role in coaching both the patient and caregiver toward realizing this daily goal. Strategies to maximize adherence and to minimize adverse effects and their severity with prevention and treatment tips are a crucial part of the nursing role in the daily management of TTFields treatment. The importance of compliance should be strongly conveyed to patients by oncology nurses and treating physicians. Most recent reports suggest that patients with compliance over 90% had a median survival of 24.9 months (28.7 months from diagnosis) and a 5-year survival of 29.3%.[39] As an educator, navigator and advocate, the oncology nurse guides the cancer patient and caregiver in decision making, through initiation of TTFields therapy and adjusting to the daily challenges of treatment administration to optimize adherence and treatment outcomes.

Conclusion

TTFields and Optune represent a unique technological modality using a non-invasive at-home device for the effective treatment of GBM and cancerous tumors. Oncology nurses are situated to become important educators and advocates for the patient and caregiver on the adherent use and management of this new and evolving treatment technology.

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Amino Acid PET Imaging of the Early Metabolic Response During Tumor-Treating Fields (TTFields) Therapy in Recurrent Glioblastoma

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Abstract: Tumor-treating fields (TTFields) therapy is a relatively new treatment approach for malignant gliomas. We evaluated if amino acid PET can detect an objective metabolic response to TTFields therapy in recurrent glioblastomas. PET scanning with alpha[C-11]-methyl-L-tryptophan (AMT) before and 2 to 3 months after the start of TTFields treatment showed an interval decrease of tryptophan uptake in the whole tumor (2 patients) or in a portion of the tumor (1 patient). These data demonstrate that TTFields therapy can induce an early metabolic response in recurrent glioblastoma, and this treatment response can be detected by amino acid PET.

Key Words: recurrent glioblastoma, molecular imaging, amino acid PET, Optune therapy, alternating electric fields, tumor-treating fields

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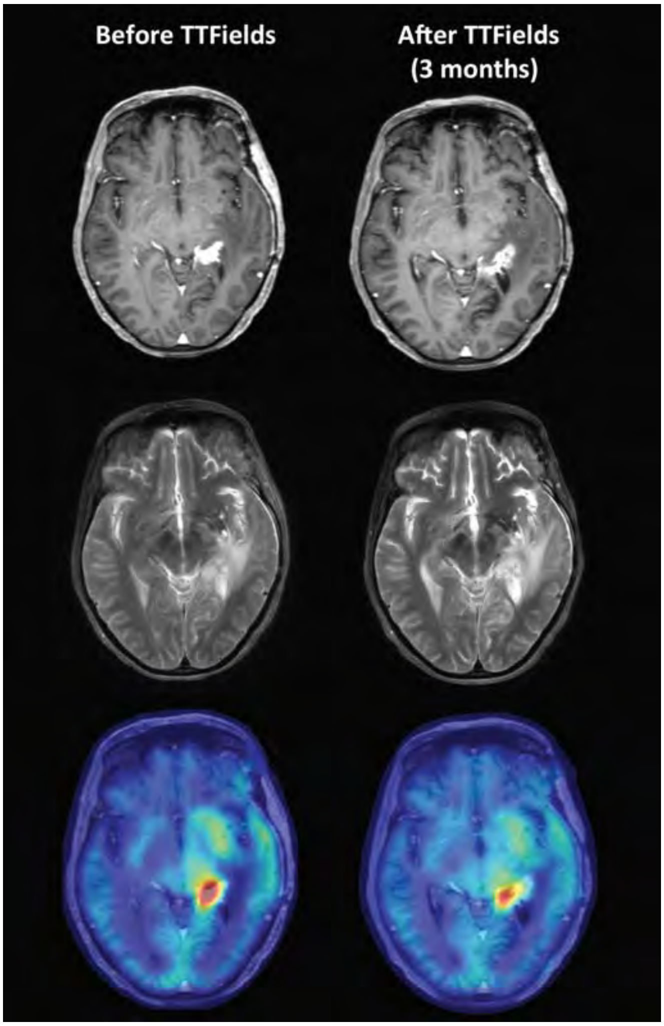

FIGURE 1. MRI (post-gadolinium T1-weighted [T1-Gad] and noncontrast T2 images) and alpha[C-11]-methyl-L-tryptophan (AMT)-PET/T1-Gad MR fusion images of a 45-year-old woman who showed MRI signs of tumor progression 2 months after completion of chemoradiation after resection of a left temporal lobe glioblastoma. Maintenance temozolomide therapy was continued and tumor-treating fields (TTFields) therapy was started after an AMT-PET scan acquired under a research protocol approved by the institutional review board.[1–3] Alpha[C-11]-methyl-L-tryptophan SUV in the contrast-enhancing mass was 5.0, consistent with active tumor.[2] After 3 months of TTFields treatment, follow-up AMT-PET scan showed decreased tumoral SUV (3.7). T1-Gad MRI showed stable contrast enhancement during the same period and in subsequent follow-up scans. Tumor-treating fields therapy for newly diagnosed and recurrent glioblastomas applies low intensity, intermediate frequency (100 kHz-1 MHz), alternating electric fields that have antiproliferative properties.[4,5] The treatment is delivered by the Optune® device with a recommended usage of at least 18 hours per day (75% compliance).[6] In a phase 3 clinical trial for recurrent glioblastomas, TTFields treatment showed equivalent efficacy when compared to active chemotherapy.[7] A randomized clinical trial also demonstrated a 5-month overall survival benefit from maintenance TTFields therapy plus temozolomide compared to temozolomide alone in supratentorial newly diagnosed glioblastoma after completion of chemoradiation.[8] Imaging studies evaluating response to TTFields treatment have been limited and confined to MRI.[9,10] The overall MRI tumor response rate was approximately 15%, and radiographic response developed slowly with a median of 5 months. Overall survival was longer in responders than in nonresponders. The present case and 2 additional patients, shown on Figures 2 and 3, demonstrate that amino acid PET may be more sensitive than MRI to detect early therapeutic responses to TTFields therapy, as metabolic effects can develop within 3 months after treatment initiation.

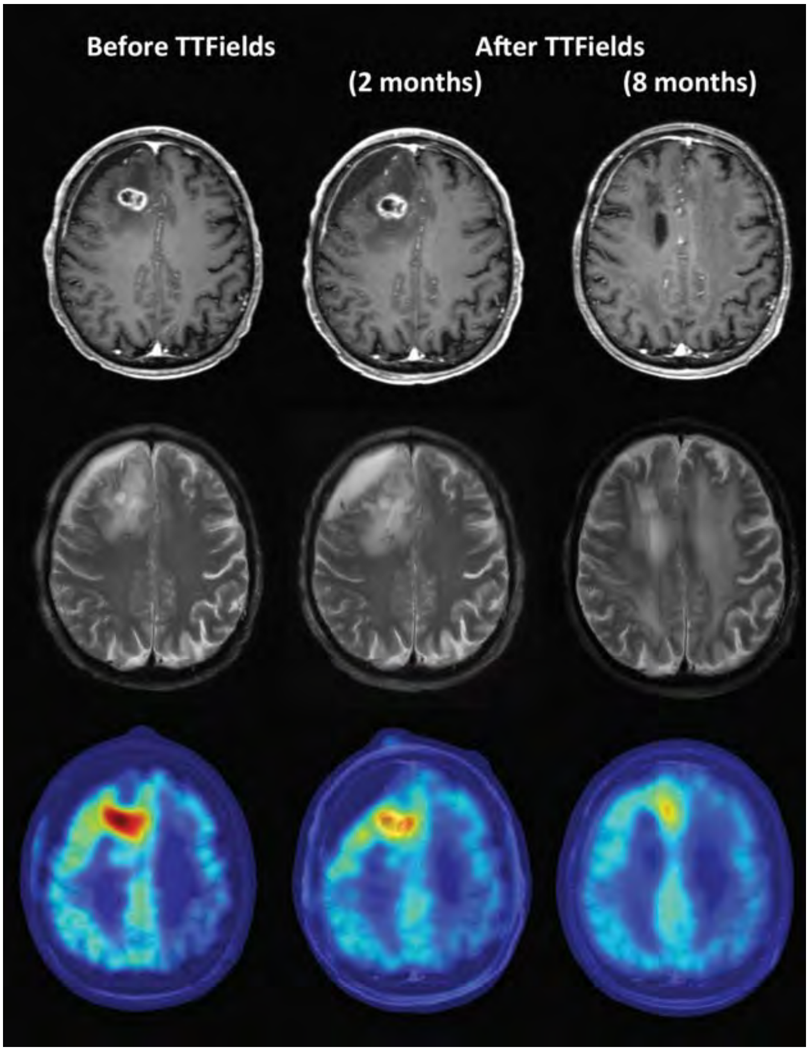

FIGURE 2. MRI (T1-Gad and T2) and AMT-PET/T1-Gad MR fusion images of a 64-year-old man with an aggressive right frontal glioblastoma that progressed during postsurgical chemoradiation (proven by histopathologic examination). Tumor-treating fields treatment was started shortly after MRI and AMT-PET scan results were consistent with further tumor progression. Baseline AMT-PET showed an SUV of 4.3 that decreased to 3.7 2 months later. MRI contrast enhancement was unchanged. Because of persistent MRI abnormalities, bevacizumab was added 1 month later while TTFields treatment was continued. A second follow-up AMT-PET 6 months later showed a further decrease of SUV (<3.0) along with interval decrease of contrast enhancement and decreased T2 signal.

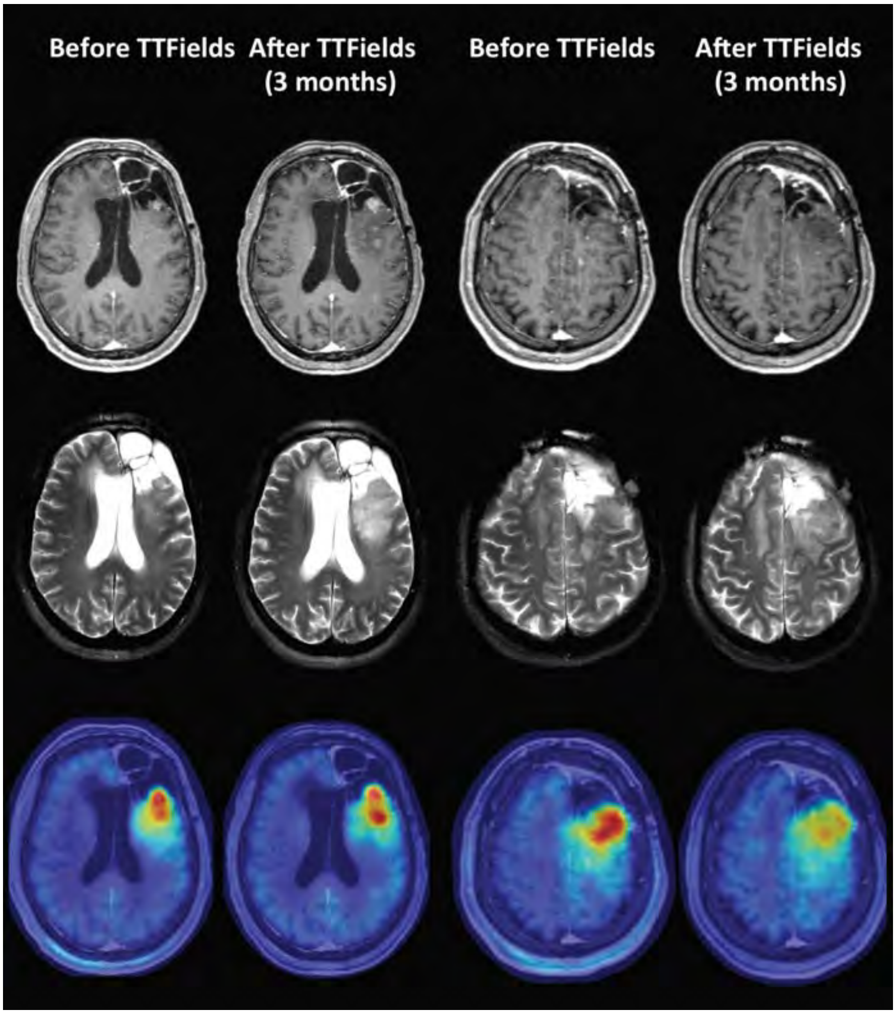

FIGURE 3. Heterogeneous metabolic response to TTFields treatment in a 51-year-old man with a recurrent left frontal glioblastoma progressing 4 months after completion of chemoradiation while on maintenance temozolomide. MRI (T1-Gad and T2) and AMT-PET/T1-Gad MR fusion images obtained at baseline and after 3 months of TTFields therapy suggested some progression. However, there were intratumoral differences in metabolic changes. Whereas the lower tumor portion showed an expansion of the area with contrast enhancement and high AMT uptake (first and second image panels), the upper tumor portion showed an interval decrease of AMT SUV from 4.9 to 3.8 (third and fourth panels).

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Review

Tumour treating fields in a combinational therapeutic approach

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ABSTRACT

The standard of care for patients with newly diagnosed Glioblastoma multiforme (GBM) has remained unchanged since 2005, with patients undergoing maximal surgical resection, followed by radiotherapy plus concomitant and maintenance Temozolomide. More recently, Tumour treating fields (TTFields) therapy has become FDA approved for adult recurrent and adult newly-diagnosed GBM following the EF-11 and EF-14 trials, respectively. TTFields is a non-invasive anticancer treatment which utilizes medium frequency alternating electric fields to target actively dividing cancerous cells. TTFields selectively targets cells within mitosis through interacting with key mitotic proteins to cause mitotic arrest and cell death. TTFields therapy presents itself as a candidate for the combinational therapy route due to the lack of overlapping toxicities associated with electric fields. Here we review current literature pertaining to TTFields in combination with alkylating agents, radiation, anti-angiogenics, mitotic inhibitors, immunotherapies, and also with novel agents. This review highlights the observed synergistic and additive effects of combining TTFields with various other therapies, as well highlighting the strategies relating to combinations with electric fields.

INTRODUCTION

The use of electric fields for the treatment of neurological disorders pre-dates its use in the treatment of glioma [1]. Electric fields administered to the brain demonstrate profound effects specific to the parameters used – being frequency (Hertz – Hz), intensity (Volts – V) and pulse-width (Seconds – s). This review will focus on the Optune™ technology relevant to the treatment of brain tumours.

OPTUNE™ (FORMERLY KNOWN AS NOVOTTF-100A)

The Optune system is a US Food and Drug Administration (FDA) approved novel anti-mitotic device that delivers continuous alternating electric fields to the patient for the treatment of primary and recurrent Glioblastoma multiforme (GBM). Optune is indicated for patients which are of at least 22 years of age, with histologically confirmed supratentorial GBM (WHO grade IV astrocytoma [2]). Optune in combination with Temozolomide (TMZ) has been approved for use in adult patients with newly diagnosed GBM following maximal safe resection, as well as completion of radiation therapy with concomitant TMZ [3].

The Optune system is composed of four transducer arrays, a field-generator, and a power source (Figure 1). The field-generator delivers electric fields through the insulated transducer arrays which are applied to the shaved scalp of the patient. The field-generator delivers pre-set electric fields (200 kHz for glioma as determined by Kirson *et al.* [4] and with a minimum field intensity of 1.0 V/cm [5] – termed tumour treating fields (TTFields))

throughout the tumour in a non-invasive manner [6]. Much progress has also been made with optimisation of transducer layout in order to deliver a more efficacious treatment to improve patient outcome. The optimal array placement on the patient's scalp is calculated using NovoTAL™ (Novocure Ltd., Haifa, Israel) simulation software, which will look to optimise field intensity within the tumour with variables such as tumour loci and patient's head measurements [7].

A single transducer array is composed of 9 insulated biocompatible ceramic disks. A conductive hydrogel is applied to the patient's shaven scalp to prevent direct contact of the ceramic disks and scalp. Thorough and frequent shaving of the patient's scalp is required for optimal contact between the transducer arrays and skin. Application of the transducer arrays to the scalp of the patients is not a sterile process, however the prescribed transduced arrays are supplied in individual sterile packages in order to reduce risk of infection. For GBM patient's, Optune TTFields therapy is delivered through two pairs of orthogonally positioned transducer arrays on the patient's scalp. These particular components are secured in place, with emphasis on continuous skin contact, by being attached to a hypoallergenic medical adhesive bandage. A single cable connects each transducer array to the portable field generator component of the Optune system [6]. A critique of the Optune system was the cumbersome nature of the field-generator, however this has been addressed with the production of a second generation design – yielding a reduction in total weight of over 50% (https://www.optune.com/hcp/therapy/system).

A number of contraindications are associated with the Optune system which could discourage uptake. Firstly, the effects of TTFields have only been studied with adults, therefore Optune TTFields therapy may only be administered to patients of 22 years or older. Patients are excluded from treatment if they have a skull defect which would restrict attachment of the transducer arrays, and also if they have known sensitivity to conductive hydrogels (https://www.optune.com/Content/pdfs/Optune_IFU_8.5x11.pdf). Medically implanted devices (such as DBS devices) were removed from the list of official contraindications due to a retrospective analysis of 1,402 patients which revealed no device related safety concerns for the 49 patients with implanted medical devices [8]. Lastly, considerations have to be made regarding patients without access to assistance with the Optune system (either a friend/relative or carer) or do not have sufficient mental competence for personal maintenance of and compliance with the system, as patients are expected to comply to the system on average at least 18 hours per day [9].

TTFIELDS MECHANISMS OF ACTION

Understanding the approach of TTFields requires familiarity with three concepts. Firstly, electric fields may be uniform – an electric field which is constant at every point in space, or non-uniform – an electric field which varies in magnitude and/or direction (convergent or divergent) at a given point in space [10]. Secondly, an electric field may be a constant field – where the source charge remains constant such that a test charge will

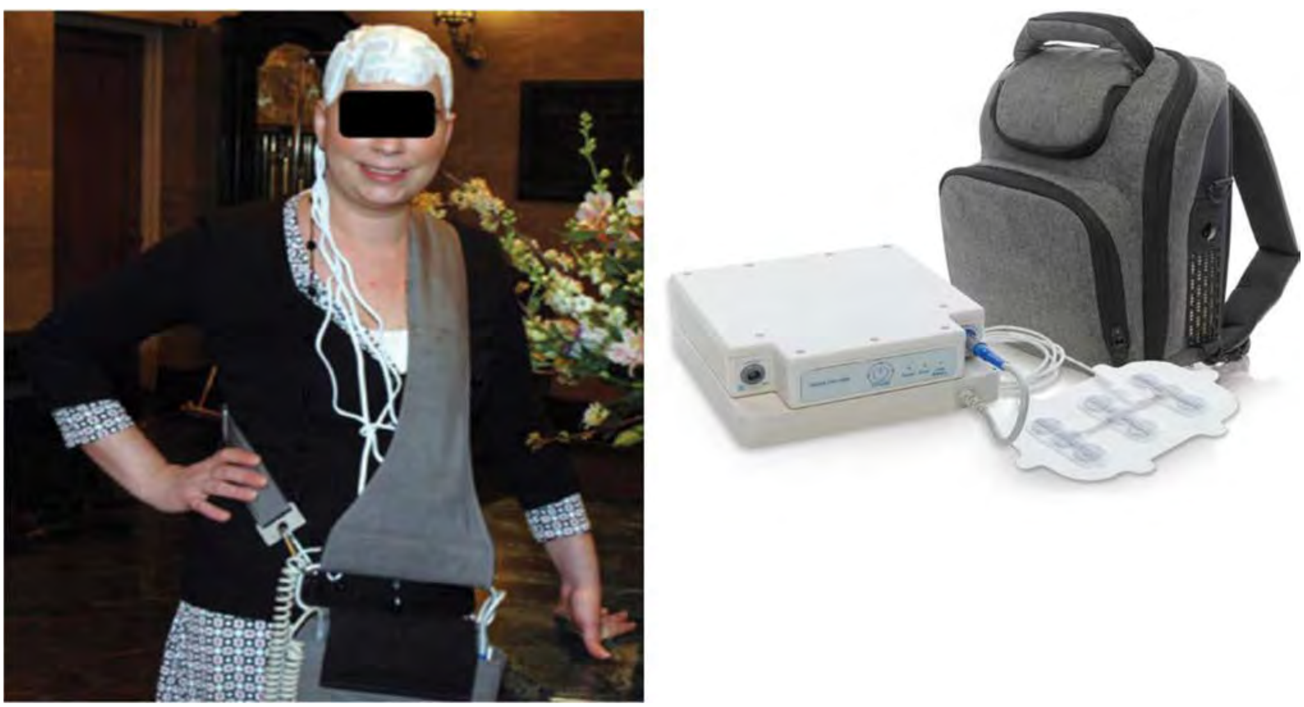

Figure 1: The Optune System. (Left) The Optune System as worn by a patient. (Right) The Optune System consisting of a field generator connected to a transducer array, with the included backpack to facilitate portability of the field generator.

converge, in a single direction, within the constant field towards the opposite polarity source. An electric field may also be a time-varying field – where the charges of the sources do not remain constant and therefore alternate space [10]. Lastly, the test charge may either be an electric monopole or an electric dipole. An electric monopole will simply alternate direction of travel along an alternating uniform field, however, an electric dipole will spin within the alternating uniform field while orientating with its current direction. Both electric monopoles and dipoles will travel towards the point of greatest electric field intensity within a converging non-uniform field – a process known as dielectrophoresis [10].

The concept of treating cancer through targeting dividing tumour cells with TTFields was originally raised by Prof. Yoram Palti, Israel Institute of Technology [4]. The initial theory was that mitotic activity of tumour cells could be disrupted with the application of alternating electrical fields and become a potential therapeutic avenue [4]. Palti and colleagues tested this hypothesis on eleven different cell lines, with multiple cancer types, and subsequently demonstrated that the formation of mitotic spindles could be disrupted by TTFields. More specifically, Palti and colleagues showed that TTFields interfered with polymerization of tubulin subunits, a necessary process within metaphase required for cell division [4]. Other notable conclusions of the study were the significance of optimising the TTFields, to a specific cancer type, to exhibit maximal effectiveness without the consequences of excessive tissue heating or stimulation. These parameters being an intermediate frequency (200 kHz) with a low intensity (1–3 V/cm) for glioma cell lines [4]. The considerations of these parameters is necessary to avoid unwanted membrane depolarization of excitable cells and tissue heating [11]. However, these undesirable stimulations greatly decline when the frequency of an alternating electric field increases above 1kHz because of the excitable membranes' hyperpolarization/depolarization cycles becoming integrated due to a membrane's excitability response time simply being too slow to handle such high frequencies [4, 11]. Conversely, exceptionally high frequencies, within the MHz range, cause greater integration of the hyperpolarization/depolarization cycles resulting in dielectric losses – electrical heating as a result of rapidly oscillating molecules [4, 11].

Anti-mitotic effects of TTFields

As highlighted previously, living cells respond to electric fields due to intracellular polar molecules being susceptible to electrical manipulation. Of particular interest is the mechanism and interactions of TTFields with these polar molecules during mitosis, as this is where TTFields may express their anti-tumour effects [4, 12–14].

Firstly, the detailed intricacies of mitosis are beyond the scope of this review. However, certain events during this process are paramount to the understanding of how TTFields function and have therapeutic potential. Before the actualisation of the metaphase-plate, paired centromeres are captured by the ends of microtubules, before becoming orientated towards their respective poles by their opposing metaphase spindles, during anaphase to become separated via cytokinesis [12, 15]. Sister chromatid separation through cytokinesis is a consequence of Cyclin B and Securin ubiquitin-mediated degradation by Cdc20 and Anaphase Promoting Complex C (APC/C) [12, 15, 16]. This APC/CCdc20 destruction complex is dependent on proper microtubule localisation and function within the anaphase and metaphase spindles [12, 15, 16]. The key point of this process is that errors that disrupt this intricate process, particularly following commitment to anaphase, are likely to be irrevocable [17]. This dependency of cancer cells on mitotic competence is the basis for a number of therapies targetting mitosis [18], and is also the basis of TTFields as previously stated, errors committed within anaphase results in a multitude of cell fates and phenotypes including mitotic catastrophe, aberrant mitotic exit, aneuploidy, multi-nucleation, mitotic slippage and apoptosis [12, 14, 19].

One of the processes which TTFields target is tubulin polymerization [4, 10, 12, 14]. Microtubules consist of polymerized tubulin dimers, arranged around a hollow core in parallel [20]. The dynamic instability of microtubules is particularly crucial for cytoskeleton remodelling which occurs during mitosis, simply put, tubulin dimers undergo expeditious cycles of polymerisation and depolymerisation. Both α-tubulin and β-tubulin are bound to guanosine triphosphate (GTP) which in turn regulates the polymerization process, and it is the hydrolysis of GTP, bound to β-tubulin, to guanosine diphosphate which favours depolymerisation [20, 21]. In summary, microtubule formation is determined by the rate of tubulin polymerization relative to the rate of tubulin depolymerisation/GTP hydrolysis. Therefore, TTFields would promote depolymerisation, given that tubulins are among the most polar molecules within cells [10, 22], by causing misalignment of tubulin subunits as they become forced to align with the electric field rather than their respected microtubule filament axis [10, 22]. This in turn promotes hydrolysis of GTP to GDP at the positive end of the microtubule, dissociation of tubulin subunits and overall microtubule disruption [20].

Given that TTFields affect mitosis through their effects on proteins that possess a high dipole moment and significance within the mitotic process, it would be reasonable to assume that TTFields would interact with a large number of proteins. Recently, Gera *et al.* showed the effects of TTFields on other key mitotic proteins and that TTFields express a more diverse

interaction than once thought [12]. Gera *et al.* focussed on the Septin heterotrimer (Referred to as Septin from now on), composed of Septin 2, 6 and 7, due to its large dipole moment of 2711D as well as its interaction with the cytokinetic cleavage furrow (CCF) formation [12]. Of note is the dipole moment of Septin which is larger than the dipole moment of tubulin dimers (1660D). Other components of the CCF were excluded from the analysis due to incomplete crystal structure information prohibiting dipole moment calculations, including Anillin and PLK1 [12]. The significance of Septin resides within the anaphase spindle midline and CCF, where through cooperation with Anillin, stabilisation of microtubule structures and the boundaries of the CCF contractility are distinguished [12, 23, 24]. Anillin functions as an adaptor protein for binding of ECT2 to the Septin/Anillin complex to facilitate both regulation and localisation of the CCF and for stability of anaphase spindle midlines [12, 24]. Septin/Anillin regulation of CCF contraction is through crosslinking actin, myosin II and RhoA [25, 26] to facilitate actin-dependent myosin contraction at the CCF [27]. In a similar fashion as tubulin, TTFields would exert rotational stress on Septin, and most likely many other proteins involved within CCF formation/regulation and progression through anaphase.

Lastly, in combination with previously discussed protein interactions, TTFields also disrupt mitosis through membrane blebbing at times coinciding with the onset of anaphase [10, 12, 22]. The most probable causes of such violent blebbing observed as a response to TTFields would be; i) aberrant localisation of CCF contractile elements, producing ectopic cleavage furrows [12] and ii) dielectrophoretic forces acted upon the CCF [4, 10, 12]. TTFields in combination with the mitotic cell's morphological changes (a resemblance to an hourglass) during the formation of the two daughter cell produces a non-uniform intracellular electric field, with the highest electric field density at the CCF directly between the dividing cells [22]. As described previously, sufficiently polar organelles and other macromolecules will gravitate towards the point of the greatest electric field intensity – the CCF, further disrupting the intricate mitotic process. It has been noted that these mechanisms are responsible for membrane disruption analogous to membrane blebbing [4, 10, 12, 28].

Overall, these results demonstrate how TTFields appear to affect mitotic cells throughout the latter stages of/and subsequent to metaphase [12, 29]. Literature has also demonstrated that the anti-mitotic effects of TTFields operates in both a p53-dependent [12] and –independent [30] manner. Also, this presents TTFields as a 'new wave' mitotic inhibitor due to the metaphase/anaphase specific disruption paradigm, where other mitotic inhibitors and traditional therapies mediate anti-tumour effects by triggering the G1/S or G2/M checkpoints of the cell cycle [12, 31, 32]. This could potentiate a synergistic effect of TTFields with other therapies affecting mitosis in combination from a more 'complete' coverage of the mitotic cycle.

TTFIELDS IN BRAIN TUMOUR CLINICAL TRIALS

The first-in-human pilot trial was conducted between 2004 and 2007 following encouraging *in vitro* and animal study data. The study assessed the safety and efficacy of TTFields therapy using the NovoTTF-100a system in 10 patients with recurrent GBM [13]. Overall; the patients had a median overall survival (OS) of 14.4 months, a 1-year survival rate of 67.5% and a median time until tumour progression of 6.0 months [13]. Notably, there were 2 patients who demonstrated an 84 and 87 month survival from TTFields therapy initiation with no radiological or clinical evidence of recurrent disease [33]. The most common side effect associated with the NovoTTF-100a system was contact dermatitis, which will be a recurrent theme with TTFields therapy, which results from hydrogel-induced localised irritation of the scalp underneath the transducer arrays of the NovoTTF-100a [33].

Recurrent GBM (EF-11 Trial)

Following the trial conducted by Kirson *et al*., [13], the pivotal phase III trial was conducted between 2006 and 2009 with the primary end-point being OS [34]. The trial was seeking to assess NovoTTF-100a as a monotherapy and to compare the treatment to best physician's choice chemotherapy (BPC) for recurrent GBM patients (n = 237). The patients of the trial were randomized (1:1) to TTFields monotherapy (n = 120) or BPC (n = 117); patients of the BPC arm were administered either a single agent or combinational therapy regime containing; Bevacizumab (31%), Irinotecan (31%), BCNU/CCNU (25%), Carboplatin (13%), TMZ (11%), PCV (9%), other agents (7%) or none received (3%). Balance was achieved between treatment arms in regard to patient characteristics; 90% of patients were at second or more recurrence, the patient's median age was 54 years and 19% of patients had previously been treated with Bevacizumab [34].

NovoTTF-100a therapy demonstrated very similar efficacy to the chemotherapies selected by the physicians, with the NovoTTF-100a arm having a median OS of 6.6 months compared to 6.0 months for the BPC arm (Hazard ratio (HR) = 0.86 [95% Confidence interval (CI), 0.66 – 1.12]; p = 0.27). Again, this was true for the progression-free survival (PFS) and the overall response rate. The PFS at 6 months was 21.4% for the NovoTTF-100a arm versus 15.1% for the BPC arm (HR = 0.81 [95% CI, 0.60–1.09]; p = 0.13), with the overall response rate being 14.0% and

9.6% (p = 0.19) for the NovoTTF-100a and BPC arms respectively [34]. However, differences between the treatment modalities become apparent when considering their respective safety profiles. A greater frequency of systemic toxicities, including Grade 3/4 haematological (17% of patients), gastrointestinal (17%), and infections (8%) was apparent in the BPC arm compared to the NovoTTF-100a demonstrating a 4%, 3% and 4% frequency of occurrence (p < 0.05; Fisher exact test) [34]. Quality of life was also observed to be higher in the NovoTTF-100a arm with regards to social, cognitive and emotional functioning, however, self-reported physical functioning was slightly worse than the BPC arm [34]. The decline of the NovoTTF-100a treated patients' physical functioning may be due to the relatively cumbersome nature of the NovoTTF-100a system, as well as the high compliance requirements for effective TTFields therapy.

Completion of this Phase III trial and the subsequent post-hoc analyses [35, 36] gave some insight into therapeutic potential of TTFields. Firstly, NovoTTF-100a therapy has similar efficacy as chemotherapy for patients with recurrent GBM but with a far more favourable side-effect profile [34]. Secondly, compliance with the NovoTTF-100a system was the main predictor of improved OS for patients. Kanner *et al.* reported a significantly longer median OS for NovoTTF-100a treated patients when compliance of 75% or greater is achieved (i.e. mean compliance of 18 hours or more per day) with a median OS of 7.7 months for the ≥75% compliance patients versus 4.5 months for the <75% compliance patients (p = 0.042). Interestingly, this post hoc analysis also described a significant stepwise correlation between median OS and compliance, with median OS of 5.8, 6.0 and 7.7 months for <60%, 60%–79%, and 80%–99% compliance, respectively (p = 0.039) [35]. Lastly, this particular Phase III trial was the first and only trial to date directly comparing bevacizumab efficacy to another monotherapy in recurrent GBM patients.

Newly-diagnosed GBM (EF-14 Trial)

Optune therapy was more recently tested in a Phase III trial for newly-diagnosed GBM patients after receiving their initial treatment as per the Stupp protocol [3]. The GBM patients (n = 700) were randomized 2:1 to either the TTFields with adjuvant TMZ or TMZ monotherapy arms, respectively. The primary end-point of the trial was achieved at the interim as PFS in the intent-to-treat (ITT) population was significantly greater for the TTFields plus TMZ arm versus the control. The secondary end-point of the trial would have been achieved if the median OS of the per-protocol treated population was significantly greater in the TTFields plus TMZ arm relative to the TMZ monotherapy arm [37]. Analysis of the first patients (n = 315) at the pre-specified interim after an 18 month minimum follow up demonstrated increases in median OS and PFS. Of note, the Independent Monitoring Committee for the trial recommended that the trial be terminated at the pre-specified interim due to perceived survival benefit of TTFields with TMZ. This resulted in the patients of the TMZ monotherapy arm being provided with access to Optune therapy [37].

The median OS for the TTFields plus TMZ arm was 19.6 months versus 16.6 months for the TMZ monotherapy arm (HR 0.75; log-rank p = 0.034) in the ITT population, and 20.5 months versus 15.5 months (HR 0.67; log-rank p = 0.0072) in the as per-protocol population. The median PFS in the ITT population was 7.1 months versus 4.0 months (HR 0.6; log-rank p = 0.0014) for the TTFields plus TMZ and the TMZ monotherapy arms, respectively [37]. As with the EF-11 trial, the addition of TTFields therapy did not produce any significant increases in systemic toxicities relative to chemotherapy alone. This was too be expected as TTFields were localised to the head, but similarly, this was associated with a significant increase in localized skin toxicities; 43% of patients receiving TTFields therapy experienced mild to moderate skin irritation, as well as 2% experiencing severe skin reactions (Grade 3) [37]. The overwhelming majority of these toxicities are skin rash/irritation based, and the nature and incidence rates of these toxicities in further studies are described here [38]. These TTFields associated dermatological toxicities may be managed prophylactically, as well as being treated should toxicities develop. The prophylactic approaches include, but are not limited to; frequent shifting of transducer array locations to minimize direct pressure to the scalp, particular care with application of transducer arrays on surgical scars, and maximising transducer array-skin contact may also reduce skin irritation. Once any dermatological toxicity develops, topical antibiotics and corticosteroids may be applied for infections or contact dermatitis and irritation, respectively [38]. A number of these dermatological complications arise from the repetitive application and removal of the transducer arrays, compounded by additional inflammation from the hydrogel used to cover the ceramic disc portion of the transducer arrays, as well as additional moisture from sweat [6, 38].

However, more recent reports on the trial's mature data have shown improved patient survival following treatment, which follows trends seen at the interim analysis [37]. The median OS from initial randomisation is 20.9 months for TTFields/TMZ versus 16.0 months for TMZ alone treated patients (HR 0.63; log-rank p = < 0.01) [1]. Interestingly, this improvement to survival was also seen across 2, 3 and 4 year survival of patients in TTFields/TMZ versus TMZ alone; with the respective rates of 43% and 31%, 26% and 16%, and 13% and 5% (p = < 0.05 for all time points) [1].

TTFIELDS IN COMBINATIONAL THERAPY

Alkylating agents

In accordance with the current standard of care, TMZ is used in combination with RT for patient benefit [3]. Two relevant highlights of this randomized phase III are apparent; firstly, the combinational therapeutic route produced a significant increase to both median OS (12.1 to 14.6 months) and 2-year survival (10% to 27%), secondly, a genetic determinant of benefit from TMZ was present in the form of methylation status of O-6-methyl-guanine-DNA methyltransferase (MGMT) [3]. Similarly, phase III studies concerning elderly patients, showed that patients expressing a methylated MGMT status benefitted greatly from TMZ treatment, although not in combination with RT, further emphasises genetic predisposition to therapeutic response [39, 40]. MGMT functions to remove the highly mutagenic and genotoxic O^6-methylgunanine residues caused by TMZ [41]. A negative feedback loop occurs upon MGMT-dependent repair of these methyl adducts whereby MGMT becomes irreversibly inactivated. It is in this absence of active MGMT that mismatch occurs during replication between methylgunanine and thymine and causes subsequent double-stranded breaks (DSBs) [41, 42]. Complimentary resistance mechanisms to TMZ, as well as other alkylating agents, are reviewed here [41].

Given the success of the initial trial, the EF-14 trial sought to evaluate the potential benefit of combining TTFields with TMZ compared to TMZ alone following chemoradiation in newly diagnosed GBM patients. As discussed previously, the current EF-14 trial data has shown promising additive efficacy of TTFields with TMZ [1, 37]. Silginer and colleagues investigated TTFields in combination with TMZ in pre-clinical glioma models focussing on MGMT-status and TMZ-resistance [43]. The study highlighted that TTFields' efficacy was not dependent on MGMT expression, nor was it diminished within TMZ-resistant cell lines [43]. The lack of overlap between the TTFields and TMZ-resistance mechanisms is not wholly unexpected however, as the primary mechanism of action for TTFields has yet to be shown to interact with MGMT [14, 44]. This feature of the study highlights how TTFields may be an attractive therapeutic option for patients whom would not benefit greatly from TMZ treatment i.e. patients with a negative MGMT methylation status [44].

A proposed mechanism of synergism would be that TTFields may potentially influence DNA fragment orientation to perturb DSB-repair mechanisms [45]. A common theme will emerge that TTFields in combinational therapeutic routes appear to have positive synergistic effects without any known overlapping toxicities.

Radiation therapy

Radiation therapy (RT) represents another physical treatment modality for cancer treatment. The high-energy ionizing radiation used for treatment damages the DNA of targeted cancerous cells, as well as normal cells which are adjacent to the targeted cells [46]. RT may be delivered to the patient through two different means; external beam radiation or through internal radiation sources, with external radiation being delivered via high-energy protons, photons or particle radiation [46]. Adjuvant RT would be utilised to target any residual tumour remaining following the resection albeit following a 4 week post-surgery recovery period [47]. As with other therapies, RT achieves therapeutic efficacy predominantly through a variety of DNA lesions; notably single- (SSBs) and DSBs [48]. It is these lesions which induce cell death via apoptosis and mitotic catastrophe [49, 50].

Given that TTFields influence polar molecules, TTFields should theoretically interact with the fragmented DNA strands following RT. Similar to how TTFields disrupt microtubule assembly [4, 10, 12, 14], TTFields may be able to influence DNA fragment orientation in a fashion to decrease DNA ligation to reduce the effectiveness of DNA repair mechanisms. This phenomenon has been reported on previously [45, 51] with reports of reduced clonogenic survival and cell viability despite the increased number of Rad51 and γ-H2AX foci when TTFields and radiation treatment were used in combination. This report suggests a reduction in DNA strand break repair competency due to the reduction in cell survival despite the upregulation of DNA repair markers Rad51 [52] and γ-H2AX [53]. More recently, the effects of TTFields in combination with radiation treatment were more intently interrogated, with an emphasis on timing TTFields with regards to RT [54, 55]. Kim and colleagues reported on the synergistic properties of TTFields with ionising radiation when TTFields were given prior to radiation treatment [54]. The combinational therapeutic route resulted in greater amounts of p53-dependent apoptosis, as well as produced mitotic anomalies indicative of TTFields treatment – multi-nucleated phenotype and both mono-polar and multi-polar spindle structures [14, 54]. Giladi and colleagues also investigated this combination but with TTFields following RT [55]. Again, it was shown that efficacy of RT may be increased with TTFields when administered following radiation treatment. Taken together, these reports suggest that TTFields may be used as a strategy to sensitise glioma to RT, whether TTFields is administered before or after RT. These interactions pose an interesting synergy paradigm which may be irrespective of established RT resistance and other DNA damage repair mechanisms.

Anti-angiogenics

Bevacizumab is a humanised monoclonal antibody which antagonizes Vascular endothelial growth factor (VEGF) to inhibit binding to VEGF-Receptor (VEGFR) [56]. Bevacizumab acquired US Food and Drug Administration (FDA) approval for the treatment of recurrent GBM, following two Phase II studies – [57] and [58] in 2009. In summary, both studies concluded that Bevacizumab use was associated with a higher PFS. However, subsequent studies have shown that Bevacizumab does not significantly increase median OS when administered as a front-line therapy for newly diagnosed GBM patients [59, 60]. Furthermore, Bevacizumab has been associated with a number of negative side effects; decline in neurocognitive function, gastrointestinal perforation, thromboembolic events, renal failure, hypertension, neutropenia and overall decreased quality of life [56, 59–61]. It appears that the majority of the lower-grade adverse effects appear to be indicative of VEGF disruption in non-cancerous cells.

As with other combinational therapeutic routes, TTFields combined with Bevacizumab is intriguing as both have shown promise for patients, albeit Bevacizumab only for recurrent GBMs [56], and may provide additive efficacy. Firstly, TTFields efficacy has been shown in a large phase III trial to be comparable to BPC chemotherapies, including Bevacizumab (31% of patients), but without a diverse and adverse effects profile akin to conventional chemotherapies [34]. Lastly, there has been evidence to suggest that TTFields may increase the safety profile of Bevacizumab when used in combination for treatment of recurrent gliomas [62]. Although on a small scale, Elzinga *et al.* retrospectively analysed patients (n = 20) treated with the combination of TTFields with Bevacizumab and found no instances of intracranial haemorrhage or thromboembolic events [62]. These particular events occur in 3% and 2.4–12.5% of patients treated with Bevacizumab respectively [56], although it is worth noting that spontaneous intracranial haemorrhage occurs in roughly 2% of patients without Bevacizumab treatment [56]. However, the exact molecular nature, if any, of these synergistic events has yet to be elucidated and should be a topic of future research. Lastly, bevacizumab is known to reduce vasogenic brain oedema, thereby reducing patients' dexamethasone requirements. The significance of reducing a patient's dexamethasone's dosage will be expanded upon in later sections.

Mitotic inhibitors

Given the intricate, yet inherently unstable mitotic process in proliferative cells, many inhibitors have been explored for the treatment of cancers; including anti-microtubular, anti-kinase and other molecular targets. The induction of mitotic cell death (MCD) is the rationale behind targetting mitosis in cancer cells. Dividing cells are highly susceptible to MCD when exposed to disruptive stresses [63]. It is these stresses which have the potential to activate the spindle assembly checkpoint (SAC), leading to a prolonged mitotic arrest where a number of different cell fates are actualized, albeit intra- and inter-line variations in cell fates are expected [64]. Combining TTFields with SAC inhibitors has been investigated [65], and demonstrated increased levels of apoptosis and G2/M-phase accumulation of cells.

The anti-microtubular class of mitotic inhibitors can be divided into two distinct sub classes; microtubular-stabilizing (i.e. Taxanes and Epothilones) and microtubular-destabilizing agents (i.e. Vinca alkaloids) [66]. These agents have demonstrated anti-tumour activity in a variety of tumours such as breast, non-small cell lung and ovarian cancer [67]. The microtubule-stabilizers, such as Paclitaxel, typically bind β-tubulin with high affinity to induce conformational changes which in turn results in stability of tubulin interactions [66, 68]. Conversely, the microtubule-destabilizers, such as Vinblastine, target microtubule polymerization through binding the vinca domain of both tubulin monomers and microtubules, causing the necessary conformational changes to reduce microtubule formation [66, 68]. Although dissimilar, both subclasses aim to cause MCD in a SAC-dependent manner. However, there has been limited transfer from laboratory to clinical practice for the majority of mitotic inhibitors [67]. This may in part be due to two main limitations; i) the phenomenon of mitotic slippage to circumvent mitotic arrest/MCD and ii) G2/M selective inhibition. Firstly, the polyploid phenotype typical of cells following mitotic arrest presents a paradigm where multiple cell fates are a result, with cells either succumbing to MCD in the subsequent G1 phase, senescence or existing as viable multiploidal cells [69]. The latter has the potential to produce cells with increasing degrees of instability from subsequent cell cycles, an overall increase in cellular stress, chemoresistance and is a predictor of intrinsic taxane resistance [70, 71]. The selective nature of mitotic inhibitors naturally leads to limitations in drug efficacy. Considering drug retention times as well as mitotic-specific drugs targetting mitotic machinery at the G2/M-M-phase, a large population of G1- and S-phase cells may remain refractory to the cytotoxic treatment [67]. Compounding this selectivity, the mitotic index of human tumours has been estimated to be less than 1% with mean doubling times of a range of solid tumours ranging from ~100 to ~400 days summarized by Komlodi-Pasztor *et al.* [72]. These observations of substantial doubling times and low mitotic indexes of solid tumour emphasise the necessity of chronic treatment over a period of multiple months of mitotic inhibitors. However, significant dose-limiting toxicity has been associated with tubulin-targetting agents—notably neutropenia [67, 73]—which has been a persistent challenge during the drug

development process. Therefore, improving drug half-life and/or drug delivery limitations, while simultaneously reducing the dose-limiting toxicities associated with tubulin-targetting agents, may be a promising area of investigation for improving mitotic inhibitory therapy for patients.

Mitotic kinase or associated protein inhibitors may also be a viable option for the treatment of cancer. More selective protein or kinase inhibitors seem to be attractive therapeutic options as they add more options for drug resistant tumours but have also been found to have less associated toxicities than their tubulin-associated counterparts on the whole [67, 72, 73]. Members of the Polo-like kinase (PLK) and Aurora kinase families are of particular interest to anti-mitotic therapies given their relatively restricted expression to M-phase, with minimal to null expression in G0, G1 and S-phases [73]. PLK1 and Aurora kinases are involved with multiple mitotic process including spindle assembly, cytokinesis, chromosome segregation and activation of the SAC [67, 74, 75]. Similar to microtubular associated therapies, inhibition of PLK1 and Aurora Kinase A in GBM cells appears to activate the SAC, cause MCD and mitotic arrest [76, 77]. However, given that both PLK1 and Aurora Kinase A expression appears at S-phase and peaks at the G2/M checkpoint [78, 79], combining these kinase inhibitors with the microtubule associated agents may provide greater therapeutic efficacy through a more complete coverage of the cell cycle.

TTFields may be considered as a physical novel mitotic inhibitor, so combining TTFields with biological mitotic inhibitors would appear logical. Firstly, assuming compliance to the Optune TTFields system is in the upper bracket of patient beneficial compliance (18 hours and above) [35], TTFields may overcome the limitations of mitotic inhibitor drug retention. Synergism between TTFields and mitotic inhibitors, particularly microtubule-stabilizers, has been demonstrated and novel mechanisms of increased efficacy have been postulated [80, 81]. Kirson *et al.*, suggested that as paclitaxel promotes microtubule elongation due to greater stability of tubulin dimers, TTFields would demonstrate greater influence over the microtubules due to the now greater dipole moment to increase microtubule misalignment [81, 82]. This is because the displacement vector of the positive to the negative charge is a function of an electric dipole moment. However, TTFields were shown to disrupt microtubules, through yet to be determined mechanisms, which may decrease paclitaxel efficacy in GBM [14]. More recently, Voloshin and colleagues investigated the potential for synergism of paclitaxel and TTFields in ovarian cancer cell lines [83]. The highlights of this study were the increased efficacy of TTFields when combined with paclitaxel, as well as increased accumulation of cells in the G2/M phase of the cell cycle when analysed with flow cytometry. However, accumulation of Caov-3 and OVCAR-3 cells in the G2/M phase of the cell cycle significantly increased relative to controls following 72 hours of TTFields treatment with A2780 cells fate being accumulation in the G1 phase following extended exposure to TTFields [83]. The differences between cell fates is further highlighted within the combination indexes (CI) of the cells; specifically, the A2780, OVCAR-3 and Caov-3 cell lines had Cis of 1.03, 0.81 and 0.86 respectively [83]. These data indicate a synergistic paradigm for the OVCAR-3 and Caov-3 cell lines but an additive effect for the A2780 cell line, however these observations may be due to differences in the intrinsic sensitivities of the cell lines to mitotic inhibitor treatment. Ovarian cells treated with TTFields in combination with paclitaxel also demonstrated multipolar spindle formations, which coincides with previous observations of TTFields treated cells [14].

It is conceivable the TTFields combined with microtubule-destabilizing agents, such as the vinca alkaloids, should produce a similar effect given their similar modes of action. This hypothesis gains credence from evidence of combinational therapy consisting of paclitaxel and vinorelbine, a semi-synthetic vinca alkaloid, significantly improving outcome for breast cancer patients [84]. Interestingly, evidence of combining the microtubule associated paradigms has also appeared in nature with both classes being present within the roots and rhizomes of the bat flower, *Tacca sp* [85]. Lastly, it has been shown that TTFields do not perturb localisation of PLK1 from its functional location at the anaphase spindle midline [12], but data regarding other mitotic associated proteins has yet to be collected. Therefore, there is reasoning behind combining TTFields with a number of mitotic inhibitors regardless of the mitosis stage of their action.

Immunotherapy

Just as the previously detailed therapeutic options available to GBM patients, immunological agents may have the potential for synergism with TTFields, and thus improved efficacy. Although a newly emerging phenomenon, TTFields indeed seem to induce an immune response and its anti-tumour effects may be, at least in part, dependent on the competence of the patient's immune system [29, 81, 86, 87]. Firstly, TTF-induced mitotic exit subjects the affected cells to cellular stress which among others, upregulates cell surface expression of calreticulin – an endoplasmic reticulum chaperone protein [88], a downregulation of anti-phagocytic signalling molecules such as the cell surface CD47 [89], as well as promotes secretion of HMGB1 in order to produce an immunogenic phenotype [90]. This response termed 'Immunogenic cell death' is a documented phenomenon of cancer cells when subjected to TTFields, which is dissimilar to the inherently immunosuppressive apoptosis [88, 90]. There is evidence in favour of TTFields promoting anti-tumour

immunogenicity *in vitro* and *in vivo* [81, 86, 87]. Kirson *et al.* demonstrated how TTFields may inhibit metastasis to the lungs of solid tumours but also noted that significantly greater amounts of infiltrative immune cells were found intratumourally in the metastasis [87]. Immune cells bearing the markers CD4, CD8 and CD45 were among the infiltrative cells, inferring a T-cell mediated response, but this was only true for the TTFields treated rabbits as opposed to the TTFields treated mice [87]. A few potential reasons for this discrepancy are apparent: i) species differences; ii) cancer cell line differences; iii) tumour volume differences; iv) TTFields treatment duration differences. Naturally, differences in cell lines used, as well as species would equate to differences in efficacy of treatments and competency of the immune system [91]. Lastly, significant differences in exposure durations to TTFields (1 week for mice and 5 weeks for rabbits) would account for differences in response, and indeed highlights a potential dose-dependent relationship between TTFields and an effective immune response. The significance of this dose-dependent relationship was highlighted in both the EF-11 [34] and EF-14 [1] human trials, so it should be expected that longer treatment duration should result in improved treatment outcome.

Wong *et al.* 2014 had previously observed that patients with previous low-grade glioma histology and low dosing of dexamethasone in the Phase III trial examining response rates of NovoTTF-100A as a monotherapy relative to the best physicians choice (BPC) chemotherapy had a more favourable outcome [92]. Although, it is well recognised that patients with a secondary-GBM, have a significantly more favourable prognosis and longer survival [93]. Neuro-oncologists traditionally use dexamethasone for patients with malignant brain tumours for its anti-oedema effects [94]. However, dexamethasone does exhibit profound immunosuppressive influence over patients [94], and therefore has the potential to reduce efficacy of TTFields. Wong *et al.* 2015 further examined the effect of dexamethasone on patients and determined a threshold of dexamethasone exposure for preferential survival with TTFields treatment [86]. Using an unsupervised mathematical algorithm, it was determined that patients receiving over 4.1mg/day had a 2.3-fold decrease in median OS for the TTFields treated cohort, compared to a 1.5 fold decrease in median OS for the BPC chemotherapy treated cohort [86]. A decrease in median OS was also seen with a progressive decrement in both cohorts until about 8.0 mg/day was achieved where there was no further significant effect on median OS [86]. However, it could also be assumed that patients requiring higher doses of dexamethasone may be stratified as higher-risk patients, so may therefore have a lower expected OS irrespective of TTFields.

Given that TTFields have not been shown to have any consequential effects on immune system competence, unlike traditionally used therapeutics [95], TTFields combined with immunotherapeutics gain credence for a number of reasons. Firstly, as stated above TTFields do not compromise the immune system as other agents do, potentially reducing the required dose of concurrent therapeutics. This dosage reduction should in turn reduce their inherent immune compromising nature. Secondly, the physical nature of TTFields appears to improve the infiltrative capacity of CD4 and CD8 cells in rabbit models [87], this should have clear synergistic effects with immunotherapeutics such as dendritic cells [96]. However, this potential synergism has yet to be studied and may be the key to bring the promising field of immunotherapeutics closer to the clinic for GBM patients [97, 98].

Novel agents

Undiscovered and potentially confounding synergistic properties may of course be present with a multitude of other novel or repurposed agents. This is evident through preliminary reports of TTFields with Bevacizumab [62], as well as TTFields combined with Triflouropromazine, an approved antipsychotic drug. Triflouropromazine has been identified to inhibit mitotic slippage and yet did not decrease slippage when used in combination with TTFields [99, 100]. This is particularly interesting as the treatment appeared to decrease cell counts by up to 14% when used in combination, suggesting an improvement to efficacy independent of mitotic slippage. Cells treated in combination also experienced an increase in cell size of up to 35%, a well-documented phenomenon of TTFields [101], as well as a reduced clonogenic potential of the cells [99]. These results taken as a whole may encourage further investigation into TTFields in combination with novel and repurposed drugs.

More recently, TTFields were combined with Withaferin A [102], a steroidal lactone originating from the winter cherry plant, *Withania somnifera* [103]. Withaferin A had been previously shown to have efficacy against glioma cell lines *in vitro* as well as in murine orthotopic GBM models [104]. As has been a theme with other combinational therapeutic strategies with TTFields, greater efficacy is achieved when combining TTFields with Withaferin A compared to each treatment alone [102]. The mechanisms of Withaferin A have yet to be fully described, though reports have identified Withaferin A to affect expression of transcription factors, such as NF-κB [105]. NF-κB affects cytoskeletal assembly/disassembly [106], so this most likely one of the reasons why Withaferin A is also implicated in this process [107].

Interestingly, genome-wide expression analytical approaches are emerging for TTFields treated cell lines in order to further describe mechanisms of action, but also to attempt to characterise low-responsive vs high-responsive cell lines [108]. Karanam and colleagues provided data showing differential expression of multiple canonical pathways between responsive and low-responsive cell

lines [108]. Producing similar data within brain tumour cell lines may be able to provide further direction towards more targeted combinations.

CONCLUSIONS

This review has outlined and discussed the current literature on TTFields and its interactions with various therapeutic agents. However, given the limited efficacy of TTFields as a monotherapy [34], a need for a clear mechanism of action is apparent. There already exists ample descriptive preclinical studies at the cellular level for proposed mechanisms of action [12, 14], but there is a lack of mechanistic studies across more complex models with and without a combinational therapeutic approach. TTFields research is still in its relative infancy with ongoing research, endorsed by the success of the EF-14 trial. The main benefit of concurrent TTFields therapy is predominantly focussed on the lack of overlapping toxicities, however, reports of contact dermatitis is frequent and expected. Not to be overlooked is that TTFields does not appear to perpetuate any consequences synonymous with failed therapy i.e. promoting invasion and metastasis, although this has yet to be studied in-depth.

In conclusion, TTFields offers an exciting platform for a combinational therapeutic approach whether it is with novel or standard anti-tumour agents, with hopes that future treatment strategies may utilise these unique effects associated with alternating electric fields.

CONFLICTS OF INTEREST

None.

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The Evolving Role of Tumor Treating Fields in Managing Glioblastoma

Guide for Oncologists

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Abstract: Glioblastoma (GBM) is a devastating brain tumor with poor prognosis despite advances in surgery, radiation, and chemotherapy. Survival of patients with glioblastoma remains poor, with only 1 in 4 patients alive at 2 years, and a 5-year survival rate of about 5%. Recurrence is nearly universal and, after recurrence, prognosis is poor with very short progression-free survival and overall survival (OS). Various salvage chemotherapy strategies have been applied with limited success. Tumor Treating Fields (TTFields) are a novel treatment modality approved for treatment of either newly diagnosed or recurrent GBM. TTFields therapy involves a medical device and transducer arrays to provide targeted delivery of low intensity, intermediate frequency, alternating electric fields to produce antimitotic effects selective for rapidly dividing tumor cells with limited toxicity. In the phase 3 EF-14 trial, TTFields plus temozolomide provided significantly longer progression-free survival and OS compared with temozolomide alone in patients with newly diagnosed GBM after initial chemoradiotherapy. The addition of TTFields to standard therapy improved median OS from 15.6 to 20.5 months ($P=0.04$). In the phase 3 EF-11 trial, for recurrent GBM, TTFields provided comparable efficacy as investigator's choice systemic therapy, with improved patient-reported quality of life and a lower incidence of serious adverse events. Primary toxicity associated with TTFields is skin irritation generally managed with array relocation and topical treatments including antibiotics and steroids. TTFields therapy has demonstrated proven efficacy in management of GBM, including improvement in OS for patients with newly diagnosed GBM, and is under current investigation in other brain and extracranial tumors.

Key Words: tumor treating fields, TTFields, glioblastoma, alternating electric fields, Optune

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Despite the advances in surgical techniques, radiation therapy, chemotherapy, targeted agents, and immune modulators, the survival of patients with glioblastomas (GBM) remains poor, with only 1 in 4 patients alive at 2 years, and a 5-year survival rate of about 5%.[1,2] There is also an increasing incidence of primary malignancies of the brain, although the etiology for this change is unclear.[3] Current standard of care for GBM includes maximal safe resection and conformal radiation therapy with concurrent and then adjuvant temozolomide (TMZ).[2] Several large randomized trials have investigated the role of dose-intensified TMZ (RTOG 0525)[4] or concomitant bevacizumab (AVAglio[5] and Radiation Therapy Oncology Group 0825[6]) in the initial management of GBM and reported no significant benefit in overall survival (OS).

Almost all GBMs recur, and the prognosis after recurrence is poor, with very short progression-free survival (PFS) and OS.[7–9] Various salvage chemotherapy strategies have been applied in this setting with limited success.[7–10] A novel treatment utilizing alternating electric fields, Tumor treating Fields (TTFields), has been developed as an innovative mechanism of tumor cell injury and has now been used in the management of both newly diagnosed and recurrent GBM. In this manuscript, we will review this novel technology, including its mechanism of action, evolving clinical data, current indications, and potential future applications.

WHAT ARE TTFIELDS?

TTFields therapy utilizes low intensity, intermediate frequency, alternating electric fields whose overall effects are interference with and prolongation of cell division, and disruption of cytokinesis in rapidly dividing cells, resulting in apoptosis.[11] TTFields take advantage of the electrical polarity, geometric shape, and rapid replication rate of cancer cells, and especially macromolecules within these cells to produce selective anticancer effects (Fig. 1). The optimal electrical frequency for the most effective cell kill varies by tumor type.[11,12] For recurrent GBM, TTFields are delivered at an intensity of 1 to 3 V/cm and frequency of 200 kHz. The effect of TTFields on normal cells is limited, enabling a potentially high therapeutic index to be achieved in the treatment of GBM and other malignancies.

PRECLINICAL STUDIES IN VITRO AND IN VIVO ANIMAL MODELS

The concept for TTFields as a therapeutic option for malignancy was evaluated in preclinical studies in the early 2000s. TTFields therapy was initially shown to effectively inhibit cancer cell growth in various cell lines in vitro.[13] The efficacy of TTFields depends on the intensity, frequency, and direction of the applied electric fields.[11,13] Antimitotic effects were shown to be dose-dependent in the range of 1 to 3 V/cm for rat glioma, with the strongest inhibition of cell division at

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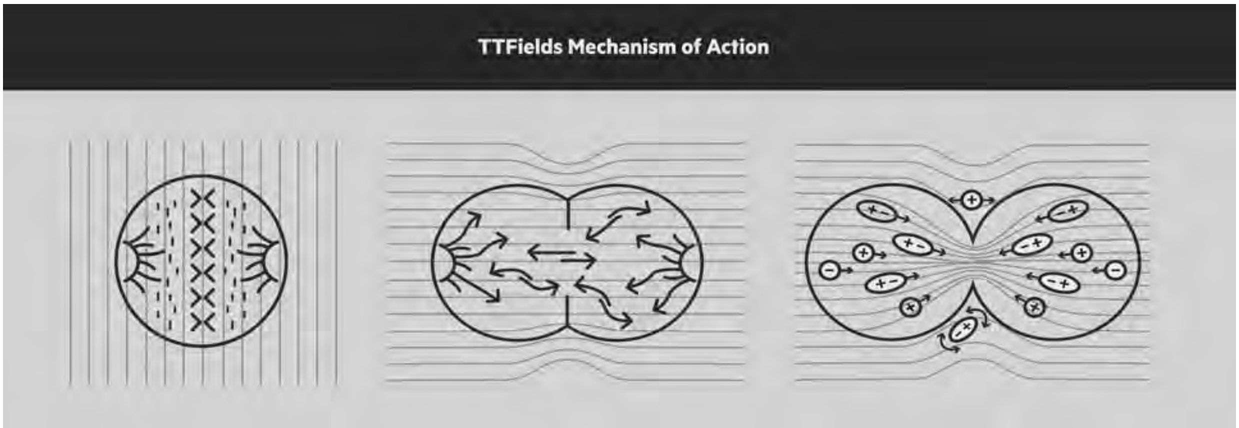

FIGURE 1. TTFields mechanism of action. The alternating electric fields interfere with mitosis leading to apoptosis and cell death. The alternating electric fields effects are interference and prolongation of cell division, and disruption of cytokinesis in rapidly dividing cells, resulting in apoptosis. Copyright Novocure, 2015. Copyright [Novocure], [Portsmouth, NH]. All permission requests for this image should be made to the copyright holder.

200 kHz.[11] This study demonstrated that the antimitotic effect was enhanced by applying electrical fields in >1 direction. As the tumor cells are not necessarily oriented in the same direction, maximal antimitotic effects are achieved when the electrical fields are parallel to the axis of cell division.[11] The antitumor effects of TTFields were confirmed in an in vivo intracranial rat glioma model, where tumor volume reductions of 42.6% (bidirectional TTFields) and 53.4% (tridirectional TTFields) were observed, compared with untreated tumors.[11] The inhibitory effect associated with unidirectional TTFields delivery was modest, whereas statistically significant tumor growth inhibition was observed with 2 or 3 directional TTFields, consistent with the in vitro results. Additional studies reported an additive antitumor effect of TTFields plus chemotherapy and radiation therapy in both in vitro and in vivo models.[14–16]

Further study has been performed on the electric field distribution and its dependence on tissue dielectric properties and anatomy utilizing a realistic head model. The researchers found that the average field strength values were about 10% higher in the tumor when incorporating anisotropy. They also concluded that the electric field in the tumor, in their realistic head model, exceeds 1 V/cm which is in the previously studied antimitotic range.[17]

TTFIELDS PILOT STUDIES

The encouraging in vitro and in vivo results led to preliminary evaluation of TTFields in patients with GBM. The initial trial examined TTFields as monotherapy in 10 patients with recurrent, TMZ-refractory GBM, comparing time to PFS and OS with historical controls.[11] The patients treated with TTFields had a median time to radiographic progression of 26.1 weeks, compared with 9.5 weeks for historical controls, and a median OS of 62.2 weeks, compared with 29.3 weeks for historical controls. Of note, 67.5% of the TTFields-treated patients with recurrent high-grade gliomas were still alive 1 year after beginning therapy.[11]

A second pilot trial tested TTFields plus TMZ in 20 concurrent newly diagnosed GBM patients who received initial therapy with standard radiotherapy and TMZ.[14] The median time to tumor progression with TTFields plus TMZ was 155 weeks versus 31 weeks with TMZ alone in the concurrent historical control group ($P=0.0002$). Median OS was >39 months in the patients treated with adjuvant TTFields plus TMZ versus approximately 14.7 months in a matched historical control group treated with adjuvant TMZ alone ($P=0.0018$). All patients treated with the TTFields had grade I-II dermatitis. There were no reported grade 3 or higher toxicities.

PROSPECTIVE RANDOMIZED TRIAL IN THE MANAGEMENT OF RECURRENT GBM

The prospective, randomized, international, phase 3 EF-11 trial compared TTFields monotherapy with investigator's choice of systemic therapy in patients with recurrent GBM.[18] I total, 117 patients were randomly assigned to TTFields monotherapy and 120 patients to investigator's choice systemic therapy.[18] The primary endpoint was OS. Secondary endpoints included PFS, PFS at 6 months, overall response rate, 1-year survival, safety, and quality of life (QoL).

Study patients treated with TTFields were instructed to wear the device ≥ 18 hours a day, with the exception of short treatment breaks of 1 hour twice a day for personal care needs. The treatment arms were well balanced, with a median age of 54 years and median KPS of 80. The vast majority (90%) of patients were at second or subsequent recurrence, with 20% bevacizumab failures before entering the trial.[18,19]

The median survival of 6.6 months in the TTFields arm and 6.0 months in the investigators'-choice chemotherapy arm was not statistically significant different. Patients treated with TTFields alone had comparable OS to that of patients who received investigator's-choice chemotherapy with various agents as monotherapy, or in combination including bevacizumab (31%), irinotecan (31%), nitrosurea (25%), carboplatin (13%), or TMZ (11%). There was no statistically significant difference in radiographic response rates, 14% versus 9.6% ($P=0.19$) between the 2 arms, that is, TTF versus control. PFS was also not different, 2.2 months for the TTFields group and 2.1 months for the investigators'-choice group ($P=0.16$).

Patients randomized to the TTFields arm self-reported a higher QoL, including improved cognitive and emotional functioning. Patients in the chemotherapy arm had statistically higher incidence of gastrointestinal, hematologic, and infectious adverse events. Severe adverse events also occurred less frequently in the TTFields-treated group compared with the chemotherapy-treated patients (6% vs. 16%, $P=0.022$). The most common device-related events experienced with

TTFields therapy were mild to moderate scalp irritation (16%) beneath the arrays. These were generally managed with topical ointments and periodic relocation of the arrays.

In a post-hoc analysis, the most significant predictor of response in the TTFields arm was treatment compliance.[20–24] Other post-hoc analyses showed that OS was significantly longer in patients whose time on therapy was 18 hours/day or greater (>75% compliance rate) than in those with a <75% compliance rate (7.7 vs. 4.5 mo, $P=0.042$). Given its mechanism of action, the antitumor effects of TTFields are immediately removed once TTFields therapy is stopped, explaining the need for continuous application. This might explain the superior survival in the patients with a more continuous utilization of the device. Post-hoc analyses also pointed to significantly higher median OS with TTFields versus investigator's choice chemotherapy for patients with Karnofsky performance status ≥ 80, tumor size $\geq 18\,cm^2$, prior low-grade glioma, and (perhaps most interesting) those who had previously failed bevacizumab therapy. These findings warrant further examination in suitably designed studies powered to better evaluate the impact of the variables on OS in recurrent GBM patients treated with TTFields.[24]

In 2011, the US Food and Drug Administration (FDA) approved TTFields therapy for recurrent GBM, based largely on the results from the EF-11 trial showing equivalent survival with TTFields therapy compared with a broad range of investigator's choice systemic therapy, together with improved patient-reported QoL and a lower incidence of serious adverse events with TTFields.

POSTAPPROVAL REGISTRY: TTFIELDS IN REAL WORLD SETTING

The impact of TTFields therapy on outcomes in patients with recurrent GBM treated outside of clinical trials has been examined using data from the Patient Registry Data set (PRiDe).[25] PRiDe is a postmarketing registry of all recurrent GBM (presumed on the basis of locally reported diagnosis) patients treated with TTFields in a real-world, clinical practice setting in the United States between 2011 and 2013. The PRiDe data set analyzed 457 patients in 91 US centers, and demonstrated a median OS of 9.6 months, significantly longer than the 6.6 months reported in the EF-11 trial ($P=0.0003$).[25] One- and 2-year OS rates were more than double for TTFields therapy patients in PRiDe than in the EF-11 trial (1-year: 44% vs. 20%; 2-year: 30% vs. 9%). Favorable prognostic factors were improved survival were first/second versus third or subsequent recurrences, higher Karnofsky performance status, and no prior bevacizumab use. There were no unexpected adverse events or safety issues. Similar to the results of prior TTFields studies, the most common adverse event was skin toxicity, which was reported in 24.3% of the patients.

PROSPECTIVE RANDOMIZED TRIAL IN THE MANAGEMENT OF NEWLY DIAGNOSED GLIOBLASTOMA

A prospective randomized phase-3 trial (EF-14) evaluated the use of TTFields in the initial management of newly diagnosed GBM, and the findings from the study led to the FDA approving TTFields in combination with TMZ for the treatment of newly diagnosed GBM in October 2015.[26] In the international EF-14 trial, 695 patients who had completed chemoradiotherapy were randomized in a 2:1 ratio to receive maintenance treatment with either TTFields plus TMZ or TMZ alone (standard adjuvant therapy). No placebo or sham device was utilized. The arms were well balanced in regards to age, performance status, resection, and MGMT promoter methylation. A prespecified interim analysis performed after the first 315 patients reached a minimum follow-up of 18 months demonstrated efficacy with acceptable tolerability and safety and led to early mandatory stoppage of the trial, as per the independent Data Safety Monitoring Committee's recommendations.

The primary endpoint of EF-14 was PFS in the intent-to-treat population.[26] OS in the per-protocol (as-treated) population was a key secondary endpoint. The prespecified interim analysis demonstrated a significantly longer median PFS in the TTFields arm versus control arm after a median follow-up of

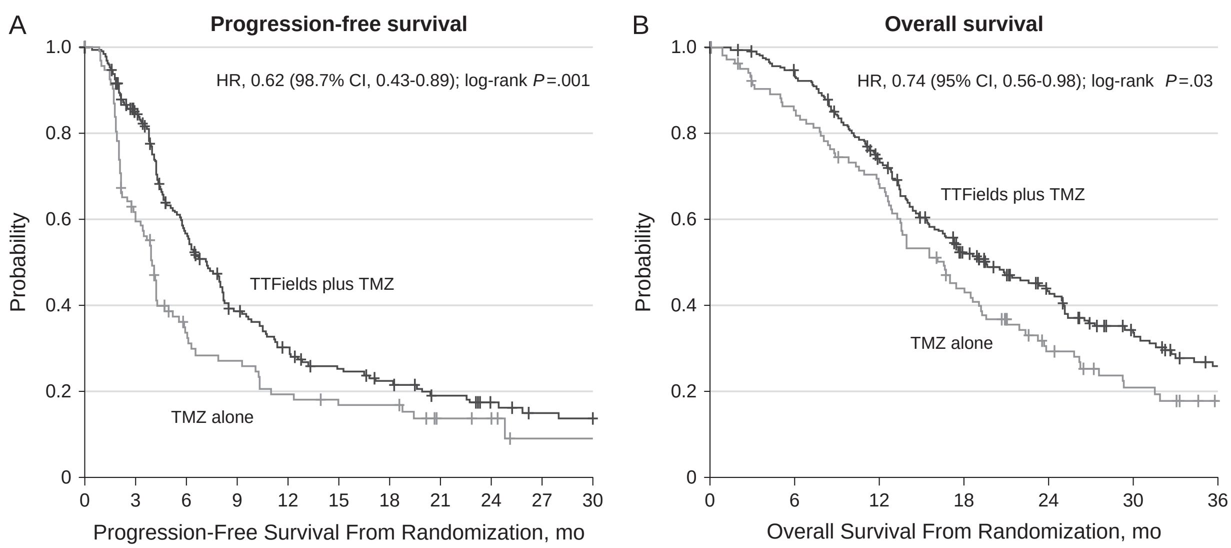

FIGURE 2. Survival curves for patients included in the interim analysis in the intent-to-treat population of EF-14. Kaplan-Meier curves for patients with GBM in the EF-14 trial, treated with TTFields/TMZ versus TMZ alone. (A) PFS (ITT) (B) OS.[26] Figure adapted with permission from Stupp et al.[26] GBM indicates glioblastoma; OS, overall survival; PFS, progression-free survival; TMZ, temozolomide; TTFields, tumor treating fields. Copyright © 2017 The Author(s).

38 months (7.1 vs. 4.0 mo; $P=0.001$; Fig. 2). The median OS in the per-protocol population was 20.5 months in the experimental arm versus 15.6 months in the control arm ($P=0.04$). The median OS in the per-protocol population was significantly longer in the TTFields versus control arm (20.5 vs. 15.6 mo; $P=0.004$). The trial was stopped before the planned accrual of 700 patients (randomized 695 patients) at the recommendation of independent data monitoring committee.[26] The results for all 695 enrolled patients with a mature minimum follow-up of 18 months and median follow-up of 36 months confirmed the results of the interim analysis that resulted in early stopping and continued to show that the addition of TTFields to TMZ confers greater benefit in PFS and OS than TMZ alone.[27]

Per protocol, OS was analyzed in the as-treated population that excluded all patients in both arms who (1) never started TMZ, (2) had a major protocol violation, (3) crossed over to the other treatment group, or (4) received TTFields outside the protocol setting. It is important to note that the randomization was not performed until after completion of the initial radiation and TMZ (chemoradiotherapy), which means patients were enrolled in the trial approximately 4 months after initial diagnosis. Historically, trials of initial management of newly diagnosed GBM measure survival from randomization before chemoradiotherapy. The randomization approach used in EF-14 was intended to minimize the effect of pseudoprogression with a time to progression endpoint, but also has the effect of excluding some of the most unfavorable patients (from both arms)—which, in turn, should be considered when comparing the OS results in EF-14 to other trials in the literature.

Three-quarters of the patients in the TTFields arm of EF-14 were considered adherent, wearing the device >18 hours per day on average during the first 3 months of therapy.[26] Two thirds of the patients randomized to the TTFields continued treatment with the device after first progression. The most common adverse event related to the device was skin irritation, occurring in 43% of patients (2% grade 3 or higher). Patients treated with TTFields were also more likely to report grade 1 or 2 mild anxiety, confusion, insomnia, and headaches, most commonly at the initiation of therapy.

TTFIELDS DELIVERY

TTFields therapy is the delivery of low intensity, intermediate frequency, alternating electric fields by 2 orthogonal pairs of transducer arrays placed on the shaved scalp of GBM patients. The device is generally worn at all times and requires an electrical power source, either direct AC plug or portable battery. Compliance can be a concern—particularly in patients with poor Karnofsky performance status. The older, first generation version of the device plus battery weighed >5 pounds which was difficult for some patients. A second generation device is now approved in the United States and Europe, weighing only 2.7 pounds including battery (Fig. 3). It is thought that the reduced weight of the second-generation device may improve patient compliance. Regular shaving of the scalp is also an essential requirement and can also cause a certain degree of noncompliance.

MANAGEMENT OF PRIMARY TOXICITY

The primary toxicity associated with TTFields is skin irritation (Fig. 4), as reported in prior clinical trials and the PRiDe data review. Skin care strategies can help maximize adherence to TTFields while maintaining QoL. Prophylactic strategies include proper shaving, cleansing of the scalp, and frequent array relocation. When skin issues arise, they can generally be managed by array relocation and topical or oral antibiotics, topical corticosteroids, and isolation of affected skin areas from adhesives and pressure.[28]

FIGURE 3. Optune with battery, charger, arrays, and carrying case. The Optune system includes electric field generator, color-coordinated arrays, charger with spare batteries, carrying case, and power outlet adapter. This image features the second-generation Optune system, currently approved for use in Europe and in the United States. Copyright Novocure, 2016. Copyright [Novocure], [Portsmouth, NH]. All permission requests for this image should be made to the copyright holder.

DURATION OF THERAPY

The antitumor effects of TTFields only occur when the device delivering them is actively in use (turned "on"). Unlike chemotherapy, there is no treatment-related "half-life" that continues after initial administration. Hence, compliance is especially critical for the effectiveness of TTFields therapy.

Of note, studies indicate that approximately 15% of patients with recurrent GBM who ultimately show durable response exhibit initial tumor growth before shrinkage.[29] Moreover, many

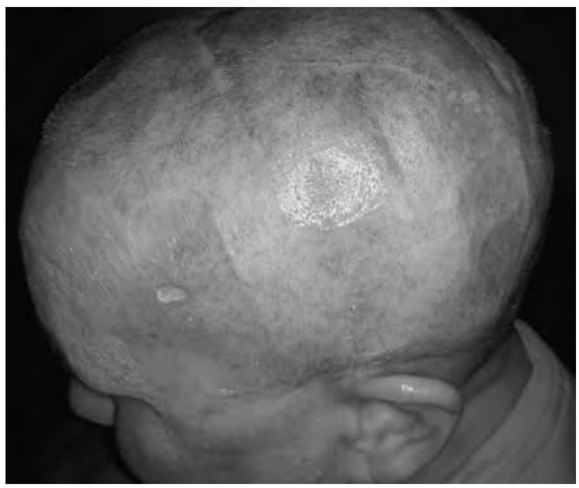

FIGURE 4. Dermatological toxicity from transducer arrays. Contact dermatitis can occur from long-term use (≥ 6 mo) of transducer arrays. These dermatitis sequelae may or may not be symptomatic. Most adverse effects could be managed using published skin care guidelines for patients receiving TTFields.[28] Reproduced with permission from Lacouture et al.[28] TTFields indicates tumor Treating fields. Copyright © 2017 The Author(s).

of these patients with slowly emerging responses have been reported to still be alive >7 years after beginning TTFields therapy.[29–31] These findings suggest that it is important to be patient and allow time when assessing the effectiveness of TTFields therapy in GBM. TTFields therapy should not be discontinued on the basis of early radiographic changes alone.[29–31] In EF-14, the device was generally worn until second progression to account for this potential transient initial enlargement of the tumor; this concept is similar to the pseudoprogression issues encountered with the use of temozolomide.

TTFIELDS ARRAY PLACEMENT

Correct placement of the transducer arrays on the shaved scalp is important for the success of the TTFields therapy. Proprietary software is used with patient magnetic resonance imaging (MRI) data to optimize array placement for maximal effectiveness (Fig. 5). In the United States, NovoTAL software is utilized for treatment mapping and planning.[32] It needs to be noted however that neither the EF-11 or EF-14 studies, nor the majority of patients in the PRiDe data set were treated using the NovoTAL array placement software.

ADOPTION OF THE TECHNOLOGY

Although supported, in the newly diagnosed setting, by prospective phase 3 data, adoption has been relatively slow in the management of patients with glioblastoma. In the fourth quarter of 2015, there were 499 new prescriptions for Optune in the United States and this had increased to 544 for the fourth quarter of 2016. Around, 55% of the new prescriptions in the fourth quarter of 2016 were for newly diagnosed patients. This was a 9% increase year over year, but represents a minority of patients with newly diagnosed GBM with only approximately 15% of newly diagnosed patients being treated with TTFields.[33]

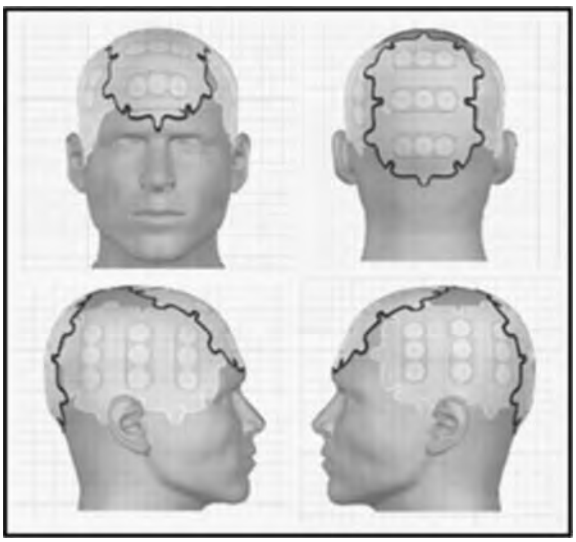

FIGURE 5. Transducer array placement for treating patients with GBM. An array map used as guidance for optimal placement of transducer arrays on the basis of tumor size and location. The array map is personalized for each patient and generated using NovoTAL System software.[32] The customization of the array layout is dependent on the patient's size and location of the tumor. GBM indicates glioblastoma. Copyright Novocure, 2015. Copyright [Novocure], [Portsmouth, NH]. All permission requests for this image should be made to the copyright holder.

There is limited published available data as to the slow rate of adoption thus far. In the authors' experiences, there is a variety of reasons for lack of adoption. The main reason is likely the newness of the technology and the need for the medical community to become familiar with the technology, device, and published data. It also is outside the usual 3 approaches to cancer therapy of surgery, radiation, and medication so there remains some skepticism on the utility of the therapy. Some clinical trials do not allow the therapy, which may also limit utilization in some of the most motivated patients. Initially, there was some question of adoption/coverage by insurance companies as well.

In addition, to utilize the device, patients are required to shave their head with no prospect for allowed regrowth, which is a deterrent. The fact that the device is visible during treatment can also reduce patient enthusiasm. Finally, the requirement for the battery pack can make the device difficult to utilize for patients with limited performance status or other physical infirmities. Generally, a committed caregiver is required to effectively manage the device with shaving, application, etc. and not all patients are able to manage the logistics associated.[33]

The slow growth of uptake may increase with continued publication of data showing efficacy, as well as, increased familiarity for both physicians and patients.

ONGOING CLINICAL QUESTIONS

TTFields are a novel cancer treatment modality for GBM. It is actively being investigated in a number of other cancer types, as well as for different GBM indications, for example, as initial therapy with bevacizumab for unresectable GBM or in combination with reirradiation or with bevacizumab (with or without reirradiation) for recurrent GBM. Ongoing and/or planned trials are exploring TTFields in low-grade gliomas as well as recurrent atypical and anaplastic meningiomas. The METIS trial is a phase 2 open-label randomized study of radiosurgery with or without TTFields for patients with 1 to 10 brain metastases from nonsmall cell lung cancer with a primary endpoint of time to first intracranial failure.[34] This trial is designed to address whether TTFields can provide the intracranial control benefit of whole-brain radiotherapy but without its cognitive toxicity, and thus includes neurocognition as a secondary endpoint.

Extracranial applications of TTFields are also being evaluated. There are trials exploring the use of TTFields in the thorax, in advanced nonsmall cell lung carcinoma, in mesothelioma, as well as for intraabdominal indications with pancreatic carcinoma and recurrent ovarian carcinoma. As preclinical data suggest synergistic benefit with radiation therapy and certain chemotherapy agents,[14,35] this is likely to be an area of active investigation.

CONCLUSIONS

TTFields, a novel anticancer therapy, has demonstrated efficacy and been approved for use in patients with GBM. The first FDA approval (2011) was for recurrent GBM, on the basis of a phase 3 study that showed TTFields exhibited similar efficacy with improved QoL and reduced rate of serious adverse events compared with investigator's choice systemic therapy. More recently, the phase 3 EF-14 international trial demonstrated the efficacy of TTFields plus TMZ versus TMZ alone as maintenance therapy following chemoradiotherapy in patients with newly diagnosed GBM. This led to the October 2015 approval of TTFields in combination with TMZ for the treatment of newly diagnosed GBM.

The neurooncology community, including many radiation oncologists, now has several years of experience with TTFields in the clinical setting of GBM. On the basis of the results of the EF-14 trial, it can be reasonably argued that TTFields should be discussed with all patients with newly diagnosed GBM as part of their initial therapy, although further studies would be useful to refine the population most likely to benefit, and more importantly identify subsets where benefit is minuscule or not present.

Treatment with TTFields can be inconvenient for patients as a result of the required application of transducer arrays directly to the shaved scalp of GBM patients for >18 hours a day, and also because of the requirement of a power supply for the unit. This lack of convenience may be at least partially compensated by the general lack of other toxicities that are associated with other focal or systemic therapies.

Although there is opportunity for further investigation of TTFields in the management of GBM, TTFields are also being actively explored as a treatment approach for patients with other brain or extracranial tumor types.

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ORIGINAL ARTICLE

Use of FET PET in glioblastoma patients undergoing neurooncological treatment including tumour-treating fields: initial experience

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Abstract

Purpose We present our first clinical experience with *O*-(2-^{18}F-fluoroethyl)-L-tyrosine (FET) PET in patients with high-grade glioma treated with various neurooncological therapies including tumour-treating fields (TTFields) for the differentiation of tumour progression from treatment-related changes.

Methods We retrospectively assessed 12 patients (mean age 51 ± 12 years, range 33–72 years) with high-grade glioma (11 glioblastomas, 1 gliosarcoma) in whom the treatment regimen included TTFields and who had undergone FET PET scans for differentiation of tumour progression from treatment-related changes. Mean and maximum tumour-to-brain ratios (TBR_{mean}, TBR_{max}) were calculated. The definitive diagnosis (tumour progression or posttherapeutic changes) was confirmed either by histopathology (4 of 12 patients) or on clinical follow-up.

Results In all nine patients with confirmed tumour progression, the corresponding FET PET showed increased uptake (TBR_{max} 3.5 ± 0.6, TBR_{mean} 2.7 ± 0.7). In one of these nine patients, FET PET was consistent with treatment-related changes, whereas standard MRI showed a newly diagnosed contrast-enhancing lesion. In two patients treated solely with TTFields without any other concurrent neurooncological therapy, serial FET PET revealed a decrease in metabolic activity over a follow-up of 6 months or no FET uptake without any signs of tumour progression or residual tumour on conventional MRI.

Conclusion FET PET may add valuable information in monitoring therapy in individual patients with high-grade glioma undergoing neurooncological treatment including TTFields.

Keywords TTFields · Amino acid PET · Glioma · Treatment-related changes · Tumour progression

Introduction

Glioblastoma (GBM) is the most common form of glioma and is also one of the most aggressive and lethal primary brain tumours, with a median survival of only 15–20 months despite maximal aggressive and multimodal therapy [1–3]. Thus, current therapeutic approaches provide modest improvement in progression-free and

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overall survival, necessitating the investigation of novel therapies.

Tumour-treating fields (TTFields) deliver low-intensity, alternating electric energy at an intermediate frequency of 200 kHz as a locoregional intervention that inhibits cell division and causes neoplastic cell death with minimal effect on normal quiescent cells [4]. It has been demonstrated that in patients with newly diagnosed GBM who have completed standard chemoradiation therapy, adding TTFields to maintenance (adjuvant) temozolomide chemotherapy significantly prolongs progression-free and overall survival [5, 6]. Furthermore, TTFields treatment is also used in patients with progressive GBM [7].

Standard MRI, including contrast-enhanced T1-weighted and T2-/FLAIR-weighted sequences, is the method of choice for brain tumour diagnostics and follow-up. In particular, changes in the extent of contrast enhancement on MRI are used as an indicator of therapy response or tumour progression [8, 9]. However, treatment-related changes such as pseudoprogression and radiation necrosis can cause disruption of the blood–brain barrier, resulting in nonspecific contrast enhancement on MRI [10–12]. Furthermore, blood–brain barrier breakdown may also result from postoperative inflammation, seizures, true tumour recurrence, or other treatment-related effects (e.g. immunotherapy). Thus, contrast enhancement resulting from increased blood–brain barrier permeability is nonspecific and may not always be an accurate surrogate for neoplastic tissue, tumour extent or treatment effect. Most importantly, treatment-related changes are of considerable importance in neurooncology because an effective treatment might be erroneously terminated too early with potentially negative effects on survival.

PET using biologically active molecules labelled with short-lived positron-emitting isotopes at micromolar or nanomolar concentrations is one of the most promising techniques for the imaging of specific molecular processes in vivo. Molecular imaging using PET may provide relevant additional information on tumour metabolism, and may also be helpful in clinical decision-making, especially in patients with equivocal MRI findings following neurooncological treatment [13, 14]. Furthermore, more widespread use of amino acid PET for the management of patients with brain tumours has been strongly recommended by the RANO group [15, 16]. The PET tracer *O*-(2-^{18}F-fluoroethyl)-L-tyrosine (FET) is a well-established ^{18}F-labelled amino acid (half-life 110 min) that shows logistic advantages over ^{11}C-methyl-L-methionine for clinical practice [17]. The clinical value of FET PET for the identification of tumour relapse has been demonstrated in numerous studies including patients with gliomas as well as patients with brain metastasis [12, 18–24].

We present our first clinical experience with FET PET in patients with GBM treated with various neurooncological therapies including TTFields for the differentiation of tumour progression from treatment-related changes.

Materials and methods

Patients

We retrospectively assessed 12 patients (mean age 51 ± 12 years, range 33–72 years; four women and eight men) with high-grade glioma (11 GBMs, 1 gliosarcoma) in whom the treatment regimen included TTFields and who had undergone a FET PET scan for the differentiation of tumour progression from treatment-related changes. For FET PET imaging, patients were referred to the Forschungszentrum Juelich (seven patients) or to the Department of Nuclear Medicine, University of Essen (five patients). This retrospective study was approved by the local ethics committee, and all patients gave written informed consent before each FET PET investigation.

PET imaging

As described previously, the amino acid FET was produced via nucleophilic ^{18}F-fluorination with a radiochemical purity of greater than 98%, a specific radioactivity greater than 200 GBq/μmol and a radiochemical yield of about 60% [25]. According to the German guidelines for brain tumour imaging using labelled amino acid analogues [26], all patients fasted for at least 4 h before the PET measurements. At the Forschungszentrum Juelich, patients underwent a dynamic PET scan from 0 to 50 min after injection of 3 MBq of FET per kg of body weight. PET imaging was performed either on an ECAT Exact HR+ PET scanner (11 scans) in three-dimensional mode (Siemens Medical Systems; axial field of view 15.5 cm, spatial resolution 6 mm) or using a BrainPET insert simultaneously with 3-T MR imaging (two scans). The BrainPET is a compact cylinder that fits in the bore of the Magnetom Trio MR scanner (axial field of view 19.2 cm, optimum spatial resolution 3 mm) [27]. Iterative reconstruction parameters were 16 subsets and six iterations using the OSEM algorithm for the ECAT HR+ PET scanner, and two subsets and 32 iterations using the OP-OSEM algorithm provided by the manufacturer of the BrainPET, with correction for random, scattered coincidences, and dead time for both systems. Attenuation correction for the ECAT HR+ PET scan was based on a transmission scan, and for the BrainPET scan on a template-based approach [27]. The reconstructed dynamic dataset consisted of 16 time frames (5 × 1, 5 × 3, 6 × 5 min).

At the Department of Nuclear Medicine, University of Essen, static FET PET imaging (five scans) was performed on a 3-T whole-body hybrid imaging system (Biograph mMR; Siemens Healthcare, Erlangen, Germany). For the

evaluation of [18]F-FET uptake, summed PET images over the period 20–40 min after injection were used for static data.

PET data analysis

Mean tumoral [18]F-FET uptake was determined using a two-dimensional autocontouring process with a tumour-to-brain ratio (TBR) of at least 1.6. This cut-off was based on a biopsy-controlled study in cerebral gliomas and differentiated best between tumoral and peritumoral tissue [28]. In order to exclude any influence of the different resolutions of the HR+ scanner and the BrainPET scanner (Forschungszentrum Juelich), a circular region of interest (ROI) with a diameter of 1.6 cm was centred on the maximal tumour uptake [19] for evaluation of the maximal FET uptake. Mean and maximum TBR (TBR_{mean} and TBR_{max}) were calculated by dividing the mean and maximum standardized uptake value (SUV) of the tumour ROI by the mean SUV of a larger ROI placed in the semioval centre of the contralateral unaffected hemisphere including the white and grey matter [26]. Tumour volumes on FET PET were calculated using a three-dimensional autocontouring process with a threshold of 1.6 using PMOD (version 3.505; PMOD Technologies Ltd.).

MR imaging

On suspicion of tumour progression, all patients underwent routine MRI (1.5 T or 3 T) with standard coils before and after administration of a gadolinium-based contrast agent (T1- and T2-weighted and FLAIR sequences). Diagnosis of tumour progression or recurrence was based on RANO criteria [8].

FET PET for differentiation of tumour progression from treatment-related changes

Based on the findings of a previous study investigating the potential of FET PET to differentiate tumour recurrence or progression from treatment-induced changes in a large series of patients with pretreated brain tumours [19], tumour progression as evaluated by FET PET was assumed when a TBR_{max} of ≥2.3 or a TBR_{mean} of ≥2.0 was present. The histological diagnosis was used as the reference to confirm the FET PET-based diagnosis of tumour progression. If histology was not available, the diagnosis was confirmed on follow-up (i.e. clinical course and results of follow-up MRI). The presence of tumour progression was assumed when clinical worsening prompted a change in treatment, if palliative care had been initiated during follow-up. or if the patient died. Treatment-related changes were assumed when a TBR_{max} of <2.3 or a TBR_{mean} of <2.0 was present. The diagnosis of treatment-related changes was confirmed on follow-up (i.e. clinical course and results of follow-up MRI) and was assumed if lesions showed spontaneous shrinkage or remained stable in size on contrast-enhanced MRI, and/or neurological deficits remained unchanged (i.e. no new neurological symptoms occurred during follow-up).

Results

All 12 patients received neurooncological treatment including TTFields during the course of the disease. Eight of the 12 patients were examined on suspicion of tumour relapse using FET PET. All of these eight patients had had previous tumour relapses prior to TTFields (one or two relapses each; Table 1). In the remaining four patients, TTFields was added to the first-line treatment regimen (patients 2, 7, 10 and 12). Two of these four patients were examined using FET PET on suspicion of tumour relapse, and the remaining two underwent baseline and follow-up FET PET imaging for treatment monitoring, and had no signs of tumour relapse (patients 2 and 7; Table 1).

Histopathological results for a definite diagnosis were available in four of the 12 patients. In the remaining eight patients, diagnosis of treatment-related changes or tumour progression was based on follow-up (clinical course and follow-up MRI). An overview of the patients' characteristics is presented in Table 1.

In patients in whom the diagnosis confirmed tumour progression (nine patients), all corresponding FET PET scans showed increased uptake (TBR_{max} 3.5 ± 0.6, range 2.5–4.4; TBR_{mean} 2.7 ± 0.7, range 2.0–4.0). In four of these nine patients, tumour progression was diagnosed histologically. Imaging and histology in a representative patient (patient 11) are presented in Fig. 1. In patients in whom the diagnosis of tumour progression was confirmed clinically (five of nine patients), the median follow-up was 4 months (range 3–6 months). Static data on FET uptake in the lesions are presented in Table 1. Furthermore, in three of these nine patients, a baseline FET PET scan prior to initiation of neurooncological treatment including TTFields was available (patients 3, 4 and 6; Table 1). Compared with baseline, either a significant increase in the metabolically active tumour volume (patient 4; Fig. 2) or a significant increase in TBR (patients 3 and 6) on FET PET were observed. In patient 3, TBR_{max} increased from 3.2 to 3.9 (22%) and TBR_{mean} from 1.9 to 2.3 (21%). In patient 4, TBR_{max} increased from 1.9 to 2.8 (47%), and TBR_{mean} from 1.7 to 1.9 (12%). In patient 4, the metabolically active tumour volume increased significantly from 9 ml (at baseline) to 42 ml (at 9 months; Fig. 2).

In two patients (patients 2 and 7), TTFields alone without any other concurrent neurooncological therapy was used as maintenance therapy. In patient 2, TTFields was started 5 months after completion of radiotherapy with concomitant and adjuvant temozolomide chemotherapy over six cycles. In this patient, TTFields was initiated at the patient's personal

Table 1 Patient characteristics

Patient no.	Sex	Age (years) at initial diagnosis	Neuropathology	Pretreatment	Treatment line on suspicion of progression/FET PET imaging	Number of previous tumour relapses	Number of FET PET scans	Main FET PET findings	Diagnosis based on FET PET	Confirmation of diagnosis	FET PET consistent with diagnosis?
1	Male	42	GBM IDH WT cMGMT methylated	First-line: resection, TMZ-RCx	Second-line: resection, TMZ, TTFields	1	1	TBR_{max} 2.2; TBR_{mean} 1.8	Treatment-related changes	Follow-up	Yes
2	Female	48	GBM NOS	n.a.	First-line: resection, TMZ-RCx, TTFields (TTFields begin 5 months after TMZ-RCx completion)	0	2	No increased uptake in either scan	No PD	Follow-up	Yes
3	Male	39	GBM IDH WT MGMT not methylated	First-line: biopsy only, TMZ-RCx	Second-line: PC, TTFields	1	2	Increase compared with baseline: TBR_{max} 22%, TBR_{mean} 21%	PD	Follow-up	Yes
4	Male	49	GBM IDH WT MGMT not methylated	First-line: resection, TMZ-RCx	Second-line: BEV, RT, TTFields	1	2	Significant increase in FET tumour volume compared with baseline	PD	Follow-up	Yes
5	Female	42	GBM IDH WT MGMT not methylated	First-line: resection, TMZ-RCx	Second-line: CCNU, TTFields	1	1	TBR_{max} 3.4; TBR_{mean} 2.2	PD	Follow-up[a]	Yes
6	Female	33	GBM NOS	First-line: resection, TMZ-RCx	Second-line: resection, RT, TMZ, TTFields	1	2	Increase compared with baseline: TBR_{max} 47%, TBR_{mean} 12%	PD	Histology	Yes
7	Female	72	GBM IDH WT MGMT not methylated	n.a.	First-line: resection, RT with concomitant TMZ, TTFields	0	3	Subsequent decrease in metabolic activity during follow-up	No PD	Follow-up	Yes
8	Male	52	GBM IDH WT MGMT methylated	First-line: resection, RT with concomitant TMZ, one cycle adjuvant TMZ, TTFields Second-line: resection, two cycles adjuvant TMZ, TTFields	Third line: CCNU, BEV, TTFields	2	1	TBR_{max} 2.5; TBR_{mean} 2.2	PD	Follow-up	Yes

Table 1 (continued)

Patient no.	Sex	Age (years) at initial diagnosis	Neuropathology	Pretreatment	Treatment line on suspicion of progression/FET PET imaging	Number of previous tumour relapses	Number of FET PET scans	Main FET PET findings	Diagnosis based on FET PET	Confirmation of diagnosis	FET PET consistent with diagnosis?
9	Male	46	GS IDH WT MGMT not methylated	First-line: resection, RT with concomitant TMZ, three cycles adjuvant TMZ, TTFields	Second-line: resection, CCNU, TTFields	1	1	TBR_{max} 3.5; TBR_{mean} 3.2	PD	Follow-up	Yes
10	Male	66	GBM IDH WT MGMT not methylated	n.a.	First-line: resection, TMZ, TTFields	0	1	TBR_{max} 3.0; TBR_{mean} 2.4	PD	Histology	Yes
11	Male	54	GBM IDH WT MGMT not methylated	First-line: resection, TMZ-RCx	Second-line: resection, CCNU, TTFields	1	1	TBR_{max} 4.4; TBR_{mean} 4.0	PD	Histology	Yes
12	Male	68	GBM IDH WT MGMT not methylated	n.a.	First-line: resection, RT with concomitant TMZ, one cycle adjuvant TMZ, TTFields	0	1	TBR_{max} 4.1; TBR_{mean} 3.6	PD	Histology	Yes

BEV bevacizumab, CCNU lomustine, *GBM* glioblastoma, *GS* gliosarcoma, *IDH* isocitrate dehydrogenase, *MGMT* O^6-methylguanine-DNA-methyltransferase, *n.a.* not available, *NOS* not other specified, *PC* procarbazine and CCNU (lomustine) chemotherapy, *PD* progressive disease, *RT* radiotherapy, *TMZ* temozolomide, *TMZ-RCx* radiotherapy with concomitant and adjuvant temozolomide chemotherapy over six cycles according to the EORTC/NCIC 26981 protocol [1], *TTFields* tumour-treating fields, *WT* wild-type

[a] On progression a change of treatment regimen was recommended to the patient; however, the patient was then lost of follow-up

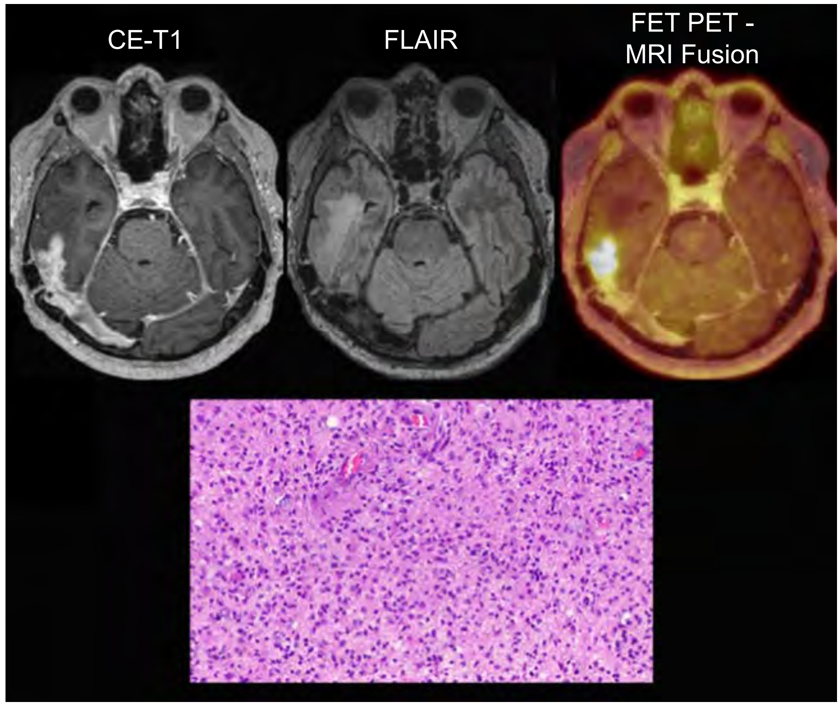


Fig. 1 Contrast-enhanced MRI, FLAIR-weighted MRI and PET-MRI fusion images (*top row*) in a 55-year-old man with glioblastoma at the time of progression treated with lomustine and TTFields (patient 11). In line with the MRI findings, FET PET shows increased metabolic activity (TBR_{max} 4.4, TBR_{mean} 4.0). Histology (haematoxylin and eosin stain, *bottom*) after resection is consistent with progressive glioblastoma

request. Prior to TTFields and 5 months later, FET PET showed no increased uptake. In patient 7, TTFields was started 4 weeks after completion of radiotherapy with concomitant temozolomide chemotherapy. Due to an immune thrombocytopenia, adjuvant temozolomide chemotherapy could not be administered. Prior to TTFields, baseline FET PET showed slightly increased metabolic activity (TBR_{max} 2.0, TBR_{mean} 1.6; Fig. 3). Follow-up serial FET PET imaging at 3 months and at 6 months showed a subsequent decrease in metabolic activity as indicated by a reduction in TBR (Fig. 3).

In contrast to standard MRI which suggested tumour recurrence (patient 1), FET PET findings were consistent with posttherapeutic changes (Fig. 4). This diagnosis was confirmed clinically; the follow-up was 6 months.

Discussion

In the present study, we evaluated the use of FET PET for the differentiation of tumour progression from treatment-related changes in patients with high-grade gliomas in whom the treatment regimen included TTFields. The main finding was that in all patients in whom histology or clinical follow-up confirmed disease progression, FET PET showed increased uptake or an increase in metabolically active tumour volume (Table 1). Moreover, in one patient FET PET and MR imaging findings were discordant and consistent with treatment-related changes (Fig. 4). Thus, the combined use of TTFields and other treatment regimens leads to similar results with respect to the ability of FET PET to differentiate tumour progression from treatment-related effects. Furthermore, in two patients treated solely with TTFields (patients 2 and 7), either serial FET PET revealed a decline in metabolic activity over 6 months or FET PET showed no uptake without any signs of tumour progression or residual tumour on conventional MRI. These data support the hypothesis that FET PET can be used to measure response to TTFields.

For decades, in patients with brain tumours, changes in the extent contrast enhancement on MRI have traditionally been used as an indicator of therapy response or tumour relapse [8, 9]. However, contrast enhancement resulting from increased blood–brain barrier permeability is nonspecific and may not always be an accurate surrogate for neoplastic tissue, tumour extent or treatment-related changes [10, 29, 30]. In order to help determine tumour progression, the use of FLAIR or T2 signal hyperintensity as a surrogate marker for nonenhancing tumour has been recommended [8]. However, differential diagnoses such as tumour-related oedema, radiation injury, demyelination, ischaemia, and infection can also result in hyperintense FLAIR or T2 signal hyperintensity, which is difficult to distinguish from nonenhancing tumour [30].

In neurooncology, many treatments may cause benign treatment-related effects that are difficult to differentiate from true tumour progression on conventional MRI. For example, treatment-related changes have been observed during and after various radiotherapy treatments (e.g. external fractionated radiotherapy, radiosurgery), chemoradiation with concurrent temozolomide, antiangiogenic therapy, and immunotherapy by blocking immune checkpoints such as CTLA-4 (cytotoxic

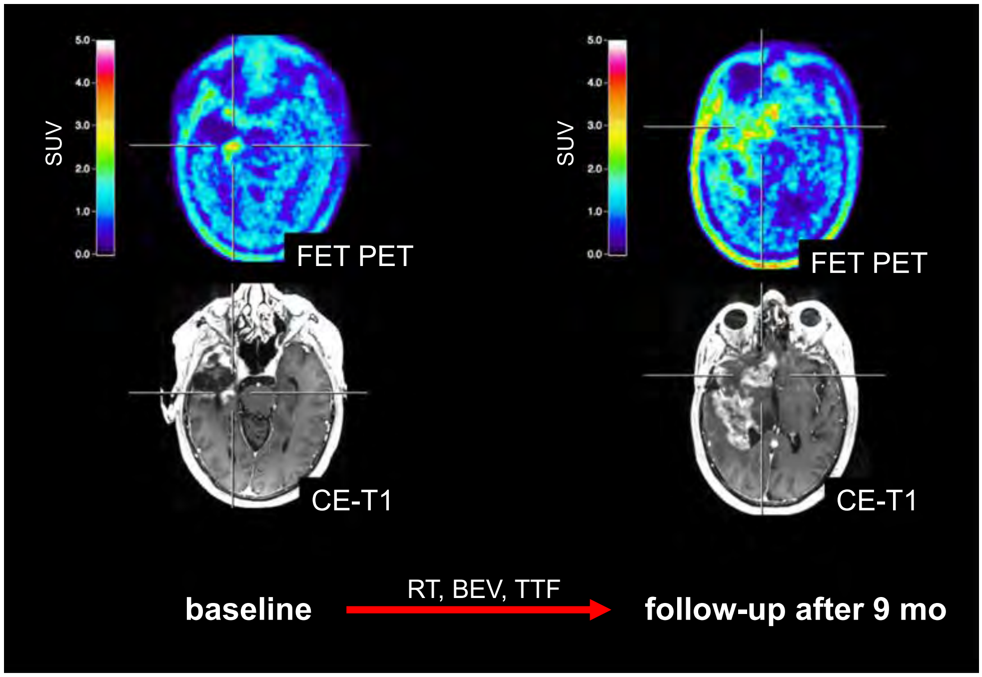
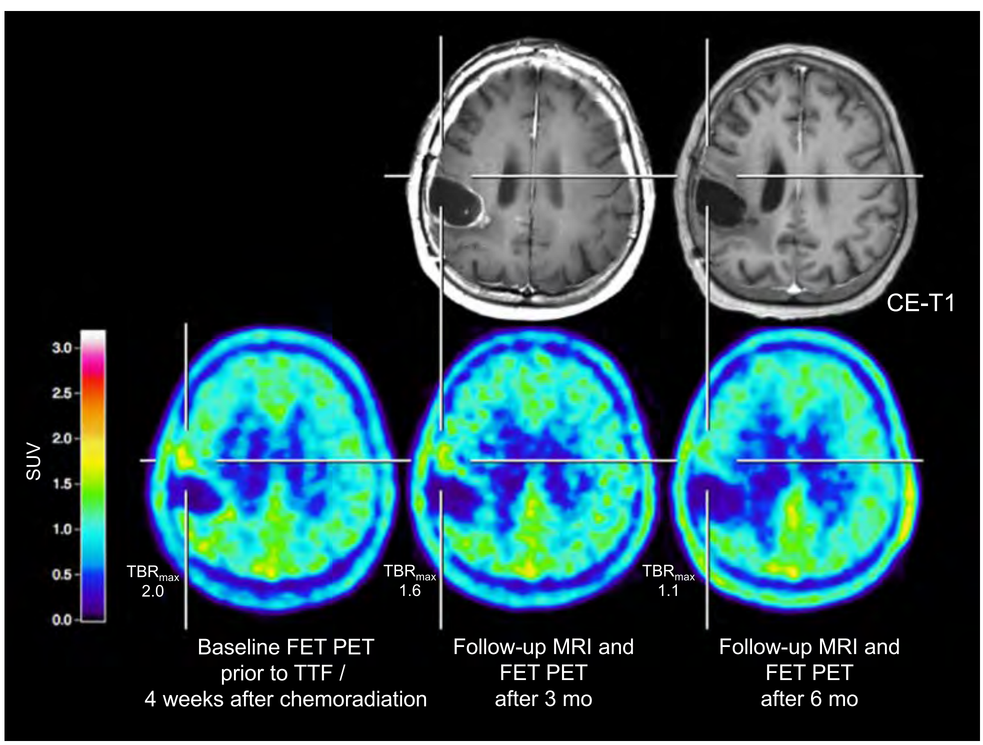


Fig. 2 Hybrid PET/MR imaging including contrast-enhanced T1-weighted images and FET PET images in a 49-year-old man with glioblastoma at the time of recurrence and at follow-up 9 months later (patient 4). In spatial correspondence with the newly diagnosed contrast-enhancing lesion (*bottom left*), the FET PET image shows a metabolically active tumour (*top left*) with increased tumour-to-brain ratios (TBR_{max} 4.0, TBR_{mean} 2.3) and a metabolically active tumour volume of 9 ml. Treatment with radiotherapy, bevacizumab and TTFields maintenance therapy was initiated. At 9 months, the MRI image shows signs of tumour progression (*bottom right*). The FET PET image shows a corresponding increase of almost fivefold in the metabolically active tumour volume to 42 ml (*top right*). The tumoral FET uptake is almost unchanged (TBR_{max} 4.0, TBR_{mean} 2.1)

Fig. 3 Imaging in a 73-year-old woman with glioblastoma (patient 7) prior to TTFields and during follow-up. Due to an immune thrombocytopenia, adjuvant temozolomide chemotherapy could not be administered. Thus, only TTF was administered and was started 4 weeks after completion of radiotherapy with concomitant temozolomide chemotherapy. Prior to TTFields, the baseline FET PET image shows slightly increased metabolic activity (TBR_{max} 2.0, TBR_{mean}1.6) without spatially corresponding contrast enhancement. The follow-up serial FET PET images at 3 months and 6 months show a decrease in metabolic activity as indicated by reductions in tumour-to-brain ratios



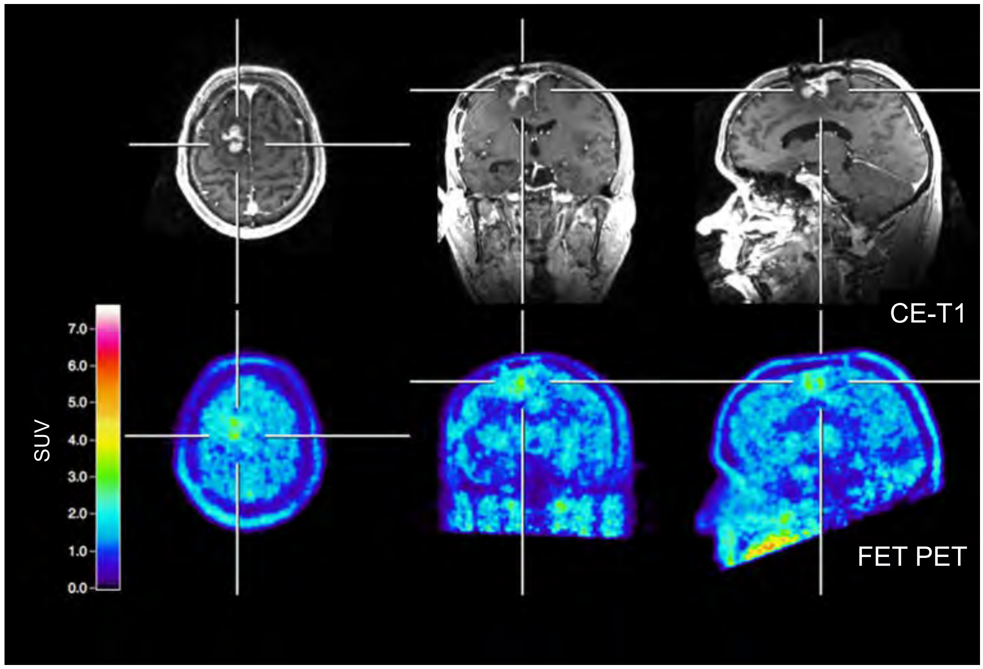


Fig. 4 Hybrid PET/MR imaging including a contrast-enhanced T1-weighted images and FET PET images in a 44-year-old man with glioblastoma treated with temozolomide and TTFields (patient 1). In contrast to standard MRI which suggests tumour recurrence (*top*), the FET PET images show slightly increased tumour-to-brain ratios (TBR_{max} 2.2, TBR_{mean} 1.8) are consistent with posttherapeutic changes (*bottom*)

T lymphocyte-associated antigen 4) and PD-1 (programmed cell death 1 receptor) [14, 31–36].

TTFields is increasingly being used for the treatment of patients with newly diagnosed GBM as well as for the treatment of patients with recurrent high-grade glioma. Additionally, in the USA the FDA has recently approved the use of TTFields for the treatment of newly diagnosed GBM. The postulated mechanism of the antitumoral effect involves the disruption of microtubule assembly during mitosis induced by the low-intensity, alternating electric energy at an intermediate frequency of 200 kHz. This blocks formation of the mitotic spindle apparatus, resulting in inhibition of cell division and neoplastic cell death [4]. Nevertheless, the effects of this postulated antitumoral mechanism on neoplastic cells especially on neuroimaging are still unclear. Additionally, data on therapy monitoring, in particular the assessment of treatment response and the differentiation between tumour progression and treatment-related changes, in patients undergoing neurooncological treatment including TTFields or TTFields therapy alone are scarce.

In order to overcome the limitations of conventional MRI, alternative imaging methods have been used for the evaluation of treatment response in patients undergoing neurooncological treatment including TTFields. In 2016, in a case report, Mohan et al. [37] described the assessment of treatment response in a patient with newly diagnosed GBM using advanced MRI techniques including perfusion-weighted MRI, diffusion tensor imaging and proton MR spectroscopy. In their patient, first-line chemoradiation with concurrent temozolomide was completed 5 months prior to TTFields initiation, and adjuvant treatment consisted a low-dose temozolomide maintenance therapy. The patient underwent serial MRI scans including a baseline scan (prior to TTFields) and two follow-up scans (1 and 2 months after initiation of TTFields). At follow-up, an increase in mean diffusivity, and decreases in fractional anisotropy, relative cerebral blood volume (rCBV) and choline/creatine ratio relative to baseline imaging were observed. The authors suggested that the changes in advanced MRI metrics are of value in the assessment of early treatment response to TTFields in combination with maintenance temozolomide chemotherapy. However, in the patient a correlation between changes in imaging parameters and outcome was not found. Furthermore, poor image quality and artefacts partially hampered advanced evaluation of the MRI data [37].

Molecular imaging using amino acid PET provides relevant additional information on tumour metabolism and is therefore helpful in clinical decision-making, especially if the MRI findings are equivocal following neurooncological treatment [13–15]. Usually, amino acid uptake is increased in tumour tissue but low or absent in treatment-related changes [18–20, 36, 38]. In view of the described limitations of conventional MRI, molecular imaging can also provide valuable information for the evaluation of treatment response [39–41]. Furthermore, the Response Assessment in Neuro-Oncology (RANO) Working Group has recently analysed the clinical role of amino acid PET in the diagnostic assessment of brain tumours, and strongly recommends the additional use of this imaging technique at every stage of brain tumour management [15].

For the evaluation of treatment response in patients with recurrent GBM undergoing TTFields therapy, the amino acid PET tracer α-^{11}C-methyl-L-tryptophan (AMT) has been used [42, 43]. All patients underwent baseline and

follow-up AMT PET imaging prior to and 1.5–3 months after initiation of TTFields therapy. In the majority of patients, objective responses in terms of metabolic tumour volume reduction were observed. The authors suggested that this decrease was related to TTFields therapy. However, all patients had other concurrent neurooncological treatment (predominantly temozolomide and bevacizumab) and it cannot be excluded that the observed reduction in metabolic tumour volumes was an effect of these therapies.

Interestingly, in the present study, in a GBM patient treated with TTFields alone we observed a decrease in metabolic activity on serial FET PET imaging (Fig. 3). This could be interpreted as a direct effect of TTFields. However, chemoradiation was completed only 4 weeks prior to initiation of TTFields. Thus, despite the fact that this patient was treated solely with TTFields, it cannot be excluded that the observed decrease in metabolic activity was an effect of chemoradiation. In another patient (patient 2) treated solely with TTFields, maintenance therapy initiated 5 months after completion of radiotherapy with concomitant and adjuvant temozolomide chemotherapy over six cycles, FET PET showed no increased uptake at baseline or on follow-up. Correspondingly, MRI showed no contrast enhancement at either time point.

Besides its retrospective character with a low number of patients, a further limitation of the present study is that the majority of patients were receiving various concurrent treatment regimens (i.e. alkylating chemotherapy, antiangiogenic therapy, radiotherapy, and combinations thereof), impeding the evaluation of the effects of TTFields using amino acid PET. However, the dataset represents a common clinical situation, and to the best of our knowledge, there is to date no larger study in the literature concerning this topic.

In summary, our findings suggest that FET PET is a reliable diagnostic tool in patients undergoing neurooncological treatment including TTFields and may add valuable additional information, particularly in patients with treatment-related changes as well as in patients treated solely with TTFields, i.e. for treatment monitoring. Further studies are warranted to confirm the clinical usefulness of FET PET in patients undergoing neurooncological treatment including TTFields or TTFields therapy alone.

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Compliance with ethical standards

Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed written consent was obtained from all individual participants included in the study.

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Cell Death Discovery

ARTICLE

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Tumor treating fields increases membrane permeability in glioblastoma cells

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Abstract

Glioblastoma is the most common yet most lethal of primary brain cancers with a one-year post-diagnosis survival rate of 65% and a five-year survival rate of barely 5%. Recently the U.S. Food and Drug Administration approved a novel fourth approach (in addition to surgery, radiation therapy, and chemotherapy) to treating glioblastoma; namely, tumor treating fields (TTFields). TTFields involves the delivery of alternating electric fields to the tumor but its mechanisms of action are not fully understood. Current theories involve TTFields disrupting mitosis due to interference with proper mitotic spindle assembly. We show that TTFields also alters cellular membrane structure thus rendering it more permeant to chemotherapeutics. Increased membrane permeability through the imposition of TTFields was shown by several approaches. For example, increased permeability was indicated through increased bioluminescence with TTFields exposure or with the increased binding and ingress of membrane-associating reagents such as Dextran-FITC or ethidium D or with the demonstration by scanning electron microscopy of augmented number and sizes of holes on the cellular membrane. Further investigations showed that increases in bioluminescence and membrane hole production with TTFields exposure disappeared by 24 h after cessation of alternating electric fields thus demonstrating that this phenomenom is reversible. Preliminary investigations showed that TTFields did not induce membrane holes in normal human fibroblasts thus suggesting that the phenomenom was specific to cancer cells. With TTFields, we present evidence showing augmented membrane accessibility by compounds such as 5-aminolevulinic acid, a reagent used intraoperatively to delineate tumor from normal tissue in glioblastoma patients. In addition, this mechanism helps to explain previous reports of additive and synergistic effects between TTFields and other chemotherapies. These findings have implications for the design of combination therapies in glioblastoma and other cancers and may significantly alter standard of care strategies for these diseases.

Background

Treatment of glioblastoma (GBM) by tumor treating fields (TTFields) is a novel, validated therapy that has become an additional modality (after surgery chemoradiation[1,2] and chemotherapy) for anti-cancer treatments[3,4].

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Originally studied in 1964 in human erythrocytes, distortions from high frequency electric fields (120 MHz) led to a reversible elongation accompanied by rotatory motions of cells[5]. Since those initial observations, intermediate frequency alternating electric fields (100–500 kHz), or TTFields, have been studied in detail[6–8]. Most recently, TTFields has been shown to prolong median survival (by 5 months) of glioblastoma patients on maintenance temozolomide chemotherapy[2,9].

The most widely proposed ("standard") mechanism of anti-cancer action by TTFields centers upon the property that tubulin subunits have intrinsic dipole moments[8]. By forcing microtubule structures to align along alternating

electric field lines through exogenous imposition of 200 kHz TTFields, the functionality of actively dividing cells is disrupted (Fig. 1a[10]) through interference with the cytoskeleton supporting mitotic spindles[7,8,11]. Such stress ulitmately promotes impaired cellular proliferation[7,8,11]. Proof of concept experiments and relevant technological developments have occurred over the past ten years[8,11], culminating in the approval by the Food and Drug Administration (FDA) of a commercial, clinical TTFields device (Optune®, Novocure Ltd., Jersey, UK) in 2011 and 2015 for the treatment of recurrent and newly-diagnosed glioblastoma, respectively[2,9,12,13].

More insights on mechanisms of action have been reported. TTFields has been shown to disrupt the localization of septins (intracellular proteins responsible for anchoring mitotic spindles during cellular division) and thereby perturb mitosis[14]. Some have reported prolongation of DNA damage by chemotherapy or radiotherapy[6,11,15] in conjunction with TTFields while others have shown effects on mitochondrial function through the swelling of mitochondrial matrices[16]. Other teams explored combination of chemotherapies (e.g., temozolomide) with TTFields in GBM patients[2,9]. Such research into combination interventions has uncovered other promising effects against glioblastoma[6,17].

Recently we have demonstrated that TTFields treatment, in conjunction with a novel anticancer compound Withaferin A, synergistically inhibited the growth of human glioblastoma cells[18]. We hypothesized that such a synergistic effect is due to increased accessibility of Withaferin A to glioblastoma cells through TTFields' capability to increase transiently, tumor cell membrane permeability (Fig. 1b). In this study, we present data that validate the hypothesis. In particular, we provide evidence to show that TTFields exposure induced greater bioluminescence in human glioblastoma cells that have been modified to express luciferase (renilla and firefly), and that this induction is due to increased permeation of the substrates (D-luciferin and coelenterazine, respectively), through the plasma membrane. Increased membrane permeability caused by TTFields exposure is also demonstrated with other membrane-penetrating reagents such as Dextran-FITC and Ethidium D.

5-ALA is a hemoglobin precursor that is converted into fluorescent protoporphyrin IX (PpIX) in all mammalian cells[19]. Malignant cells, including high-grade gliomas, have elevated hemoglobin biosynthesis, reflected in enhanced accumulation of PpIX within transformed cells and tissues[20–22]. Medical investigations thus use 5-ALA uptake (and, by consequence, its enzymatic conversion to PpIX) as a fluorescent biomarker for tumor cells[20,22]. With current technologies, it is difficult to distinguish the precise cellular margin between tumor and non-tumor tissue intraoperatively[23,24]. We show that TTFields significantly enhances the tumor to normal cell ratio for PpIX fluorescence (brought on by 5-ALA exposure and uptake), and in this manner, may better delineate tumor margins in intraoperative settings.

Finally, we present scanning electron microscopy (SEM) data that demonstrate an increase in the number and size of holes in glioblastoma cell membranes caused by TTFields exposure. Furthermore, we show that the morphology of the glioblastoma cell membrane is perturbed when TTFields are applied. Through all modalities studied (bioluminescence, fluorescence, and SEM), we found the effects of TTFields on the GBM cell membrane permeability to be reversible after cessation of TTFields exposure.

Material and methods

Cell culture studies

Two patient-derived GBM lines (GBM2[25,26], GBM39[27,28]), a commercially available human GBM cell line (U87-MG from ATCC, Manassas, VA, USA) as well as a murine astrocytoma cell line, (KR158B; a gift from Dr. Duane Mitchell of the Department of Neurosurgery at the University of Florida School of Medicine) were used for our studies.

Human U87-MG, human PCS-201 and murine KR158B glioblastoma cell lines were grown in DMEM (Invitrogen/Life Technologies, Carlsbad, CA, USA)/10% FBS/ and 1× antibiotic-antimycotic (Invitrogen/Life Technologies, Carlsbad, CA). GBM2 and GBM39 were grown in a defined, serum-free media whose composition has been described previously[18].

Seeding of cells onto glass coverslips for TTFields experiments

Briefly, cells in culture were trypsinized via standard protocols[26,29] and 10,000–50,000 single cells were suspended in 200 or 75 μL of DMEM/10% FBS/1× antibiotic-antimycotic and then were seeded onto the center of a 22 mm or 12 mm diameter glass Thermanox™ coverslips respectively (ThermoFisher Scientific, Waltham, MA, USA). The cells were incubated overnight in a humidified 95% air/5% CO_2 incubator set at 37 °C. Once the cells became attached to the coverslip, 2 mL or 1 mL of DMEM/10% FBS/1× antibiotic-antimycotic was added per well of 6-well or 12-well plates, respectively. Unless otherwise stated in the Results section, the cells were left to grow on the coverslip for two to three days (in order to ensure cells were in the growth phase) before being transferred to ceramic dishes of an inovitro™ in vitro TTFields apparatus (Novocure Inc., Haifa, Israel). Growth conditions (i.e., time cells allowed to grow under TTFields-exposed vs. unexposed conditions) are specified either in the Results section or in the corresponding figure legends.

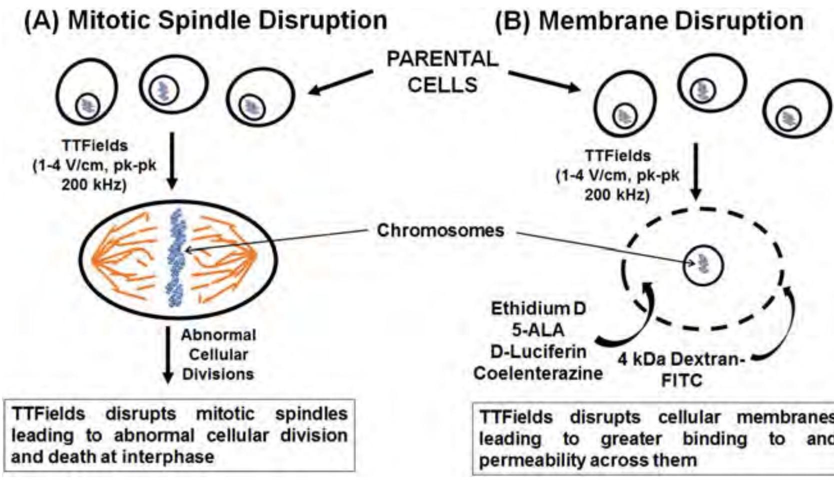

Fig. 1 a Schematic showing classical view of the alteration of the mitotic spindle during mitosis by TTFields that results in cancer cell death. **b** Schematic showing an alternative effect of TTFields on modulating the integrity and thus the permeability of cancer cellular membranes. 5-ALA, 5-aminolevulinic acid, Ethidium D, ethidium bromide, FITC, fluorescein isothiocyanate, pk, peak, TTFields, tumor treating fields

In vitro tumor treating field apparatus[30]

The coverslips were transferred to a ceramic dish of the inovitro™ system, which in turn was mounted onto inovitro™ base plates (Novocure Ltd., Haifa, Israel). Tumor treating fields at 200 kHz (1–4 V/cm) were applied through an inovitro™ power generator. Incubator ambient temperatures spanned 20–27 °C with a target temperature of 37 °C in the ceramic dishes upon application of the TTFields. Duration of TTFields exposure lasted anywhere from 0.5 to 72 h, after which coverslips were removed and processed for the appropriate bioassays (see below). For reversibility experiments, the TTFields-exposed coverslips were transferred to a regular incubator without TTFields exposure for 24 h (off TTFields period to assess for reversibility of the TTFields effect on cell membrane permeability) prior to processing for the appropriate bioassays. Culture media were exchanged manually every 24 h throughout the experiments to account for evaporation. Corresponding control experiments (no TTFields) were done by placing equivalent coverslips within 6-well or 12-well plates into a conventional humidified tissue culture incubator (37 °C, 95% air/5% CO_2) and cells grown in parallel with the TTFields-exposed coverslips. Unless otherwise mentioned, all experiments were done in at least triplicate samples per condition and per time point. A basic workflow for a typical TTFields experiment is summarized in Supplemental Figure S1.

Cell counting assay via hemocytometer

Preparation of cells for counting was achieved via established protocols[18,31] and visualized on a Zeiss PrimoVert benchtop microscope (Dublin, CA, USA). Unless otherwise stated, cell counts were done on trypsinized, single-cell suspensions with a hemocytometer and the mean of the four cell-count measurements was calculated and rounded to the nearest integer.

Bioluminescence imaging

For all bioluminescence work, we used genetically-modified GBM2, GBM39 and U87-MG whereby the glioblastoma cells were transfected with lentiviral vectors that expressed either firefly luciferase (fLuc for GBM39) or a fusion protein of GFP and firefly luciferase (GFP/fLuc for GBM2 and eGFP-fLuc for U87-MG) or a Renilla luciferase -Red Fluorescence protein fusion (RLuc-RL8 for KR158B)[32,33]. Cells were transduced using viral supernatants, and expression of luciferases was confirmed by measuring cellular luciferase activity (IVIS Spectrum; Perkin Elmer, Waltman, MA) in the presence of D-Luciferin (0.3 mg/mL final concentration) for fLuc and coelenterazine (1 μg/mL) for rLuc.

Scanning electron microscopy (SEM)

5,000 (low seeding condition) to 50,000 (high seeding condition) U87-MG/eGFP-fLuc cells or PCS-201 fibroblast cells were deposited onto 13 mm glass coverslips and then prepared for TTFields experiments under a protocol described in Supplemental Figure S1. Cells were grown under standard tissue culture incubator conditions (37 °C, 95% O_2, 5% CO_2). At the end of the TTFields-exposed and TTFields-unexposed experiments (1 day for high-seeding conditions and 3 days for low-seeding conditions), the coverslips were processed for SEM. Full details of SEM methodology are in legends of Supplemental Figure S10 and S16. All ROI analyses were performed in a blinded manner in which neither the individual responsible for SEM image acquisition nor the one performing

data analyses knew of the experimental conditions for the samples. A third individual had possession of the sample identities.

Chemical reagents

Unless otherwise stated, all chemicals were purchased from Selleckchem Inc. (Houston, TX, USA), Thermo-Fisher Scientific (Waltham, MA, USA), or Sigma-Aldrich (St. Louis, MO, USA). Purified firefly luciferin or firefly luciferase (SRE0045-2MG) as well as the Ethidium D apoptosis kit (11835246001) were purchased from Sigma Aldrich Inc (St. Louis, MO). Dextran-FITC of molecular weights 4, 20, and 50 kDa (FD4, FD20 and FD50), were purchased from Sigma Aldrich Inc. as well. 5-aminolevulinic acid (5-ALA, AAA16942ME) and the AnnexinV-APC kit (50712549) were purchased from Thermo-Fisher Scientific Inc (Waltham, MA). Supplemental Table S1 summarizes the reagents used in this study.

Statistical analysis

The PRISM 7.0 software (GraphPad Software Inc., La Jolla, CA, USA) was used to determine whether the data were normally distributed. Normally distributed data were analyzed with two-way Student's *t*-test or analysis of variance (ANOVA) comparisons of means, while non-normally-distributed data were analyzed with non-parametric analyses (e.g., Mann–Whitney *U* test comparison of medians). The level of statistical significance was set at alpha = 0.05. Bonferroni or Dunnet post-hoc corrections were employed to adjust alpha for multiple comparisons. All data are presented as range, mean ± standard deviation, median [interquartile range], or percent. In all figures, the levels of statistically significant differences are represented by: $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

Results

Induction of TTFields increases BLI in luciferase-expressing glioblastomas

TTFields (4 V/cm, 200 kHz, 0.5–24 h duration) significantly increased bioluminescence intensity (BLI) of U87-MG/eGFP-fLuc cells compared to unexposed conditions (Fig. 2a). This increase in BLI occurred as early as 30 minutes after commencement of TTFields and continued to 24 h of TTFields exposure (Fig. 2a). When ROI quantification was performed, the time course of BLI intensity for the TTFields-exposed samples was significantly elevated compared to TTFields-unexposed samples (Fig. 2b, $p < 0.0001$, two-way ANOVA, TTFields vs. no TTFields). The presence of TTFields did not significantly increase eGFP fluorescence (eGFP-FL) over the course of the experiments. When ratios of BLI over eGFP-FL was compared between TTFields vs. no TTFields samples, there was a significantly augmented ratio with respect to time of TTFields incubation for the TTFields samples (Fig. 2e, f, $p < 0.0001$, two-way ANOVA, TTFields vs. no TTFields). TTFields significantly decreased activity of purified firefly luciferase (Supplemental Figure S2, $p < 0.01$, two-way ANOVA, TTFields vs. no TTFields).

Application of TTFields over time on another patient-derived glioblastoma cell line, GBM2/GFP-fLuc also induced a time-dependent increase in bioluminescence in TTFields-exposed GBM2/GFP-fLuc cells (Supplemental Figure S3A, B, $p < 0.0001$, two-way ANOVA, TTFields vs. no TTFields). This same effect by was observed in a murine astrocytoma cell line (KR158B) that was genetically modified to express Renilla luciferase-red fluorescent protein fusion protein (Supplemental Figure S3C-D, $p < 0.0001$, two-way ANOVA, TTFields vs. no TTFields). Renilla luciferase activity is not dependent upon ATP and magnesium.

Effect of TTFields on uptake of membrane-associating reagents

Under our studied conditions, TTFields did not induce any significant degree of apoptosis in the U87-MG cells (Supplemental Figure S4). However, ethidium D uptake was significantly increased when the U87-MG/eGFP-fLuc cells were subjected to 200 kHz TTFields (Fig. 3a, $p < 0.0001$, two-way ANOVA, TTFields vs. no TTFields). Ethidium D permeates through both the plasma membrane and the nuclear membrane and intercalates into genomic DNA[34]. Thus, these findings suggest that TTFields can have an effect on the permeability of plasma membranes in U87-MG/eGFP-fLuc cells.

Dextran-FITC is known to bind and intercalate into the plasma membrane[35–37]. When U87-MG cells were subjected to 1 h of 200 kHz TTFields, there was a significant uptake of Dextran-FITC of molecular weights 4 kDa and 20 kDa, compared to no TTFields exposure, but there was no significant difference in uptake for 50 kDa Dextran-FITC (Fig. 3b–e). Over a timeframe of 0.5–24 h exposure, we found a significant increase in the uptake of 4 kDa Dextran-FITC compared to TTFields-unexposed samples (Fig. 3c, $p < 0.0001$, two-way ANOVA, TTFields vs. no TTFields), a significant increase in uptake of 20 kDa Dextran-FITC under TTFields exposure (Fig. 3d, $p < 0.01$, TTFields vs. no TTFields) and no significant difference in uptake of 50 kDa Dextran-FITC under TTFields exposure (Fig. 3e not significant, TTFields vs. no TTFields).

Effect of TTFields on 5-aminolevulinic (5-ALA) acid uptake: single U87-MG culture

We investigated the effects of TTFields on uptake of 5-ALA in glioblastoma cells. Because it is difficult to distinguish the margin between tumor and normal cells using the present 5-ALA bioassay[20,22], we hypothesized

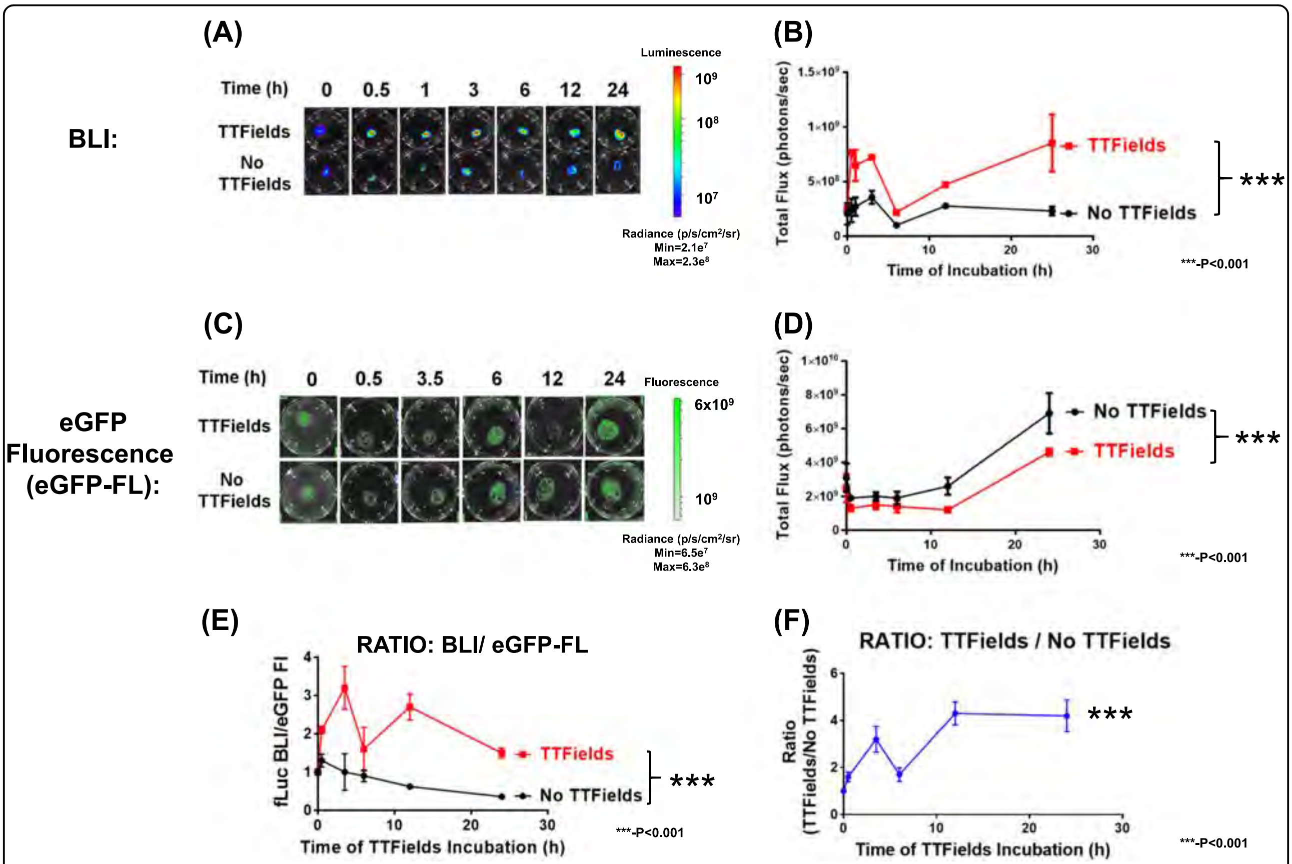

Fig. 2 Increased bioluminescence signal in U87-MG/eGFP-fLuc cells exposed to TTFields as shown by: a Representative panel of bioluminescent imaging (BLI) scans as a function of time in TTFields vs. no TTFields conditions. **b** Temporal quantification of BLI data in **a**. Significant difference (****p* < 0.001) in plot between no TTFields and TTFields. Effect of TTFields on eGFP fluorescence in U87-MG/eGFP-fLuc cells as shown by **c** time course of representative panels for TTFields-exposed vs. TTFields-unexposed U87-MG/eGFP-fLuc and **d** temporal quantification of fluorescence data in **c**. Significant difference (****p* < 0.001) in plot between no TTFields and TTFields. **e** Effect of TTFields on the fLuc bioluminescence (fLuc-BLI) over eGFP fluorescence (eGFP-FL) ratio for U87-MG/eGFP-fLuc cells as a function of length of TTFields exposure and **f** effect of TTFields exposure vs. non-exposure on the fLuc-BLI/eGFP-FL ratio as a function of TTFields exposure time (hours). For both **e** and **f**, there is a significant difference in ratio (****p* < 0.001) between TTFields exposed and TTFields non-exposed. Two-way ANOVA analysis and $n = 3$ experiments per data point in each panel (**b**, **d**, **e** and **f**)

that measurement of PpIX fluorescence would address this issue. We investigated whether permeation of 5-ALA through the cellular membrane and into the glioblastoma cells could be increased with TTFields exposure. U87-MG cells were exposed or unexposed to TTFields, each for durations of 6–24 h. TTFields exposure resulted in significantly increased uptake of 5-ALA into U87-MG/eGFP-fLuc cells as early as 6 h of TTFields exposure (Fig. 4a, b, $p = 0.047$, Student's *t*-test, TTFields vs. no TTFields) and this increase was maintained with prolonged TTFields exposure of 24 h (Fig. 4a, b, $p = 0.011$).

Effect of TTFields on 5-aminolevulinic acid uptake: U87-MG GBM on PCS-201 fibroblast co-cultures

To distinguish differences in 5-ALA uptake between glioblastoma and normal cells, a co-culture was developed where U87-MG cells were seeded in the center of a bed of PCS-201 fibroblasts and (Supplemental Figure S5) were subjected to TTFields or to no TTFields. Fluorescent and brightfield photomicrographs confirmed the presence of discrete glioblastoma (red arrows) vs. fibroblast (white arrows) cell regions in the co-culture set-up (Supplemental Figures S6–S7). When co-cultures were stained with hematoxylin and eosin (H&E), photomicrographs (Supplemental Figure S6) revealed reduced numbers of GBM cells (purple/dark pink stains) infiltrating into the fibroblast periphery (light pink) for TTFields-exposed samples. Without TTFields exposure, the GBM cells formed many pockets of adherent neurospheres (Supplemental Figure S6, dark spots on 1× images) as was previously reported[18,38]. Fluorescence images showed increased PpIX fluorescence in glioblastoma vs. fibroblast cells in the co-culture platforms (Supplemental Figure S7) that were subjected to TTFields for 6 h. PpIX fluorescence

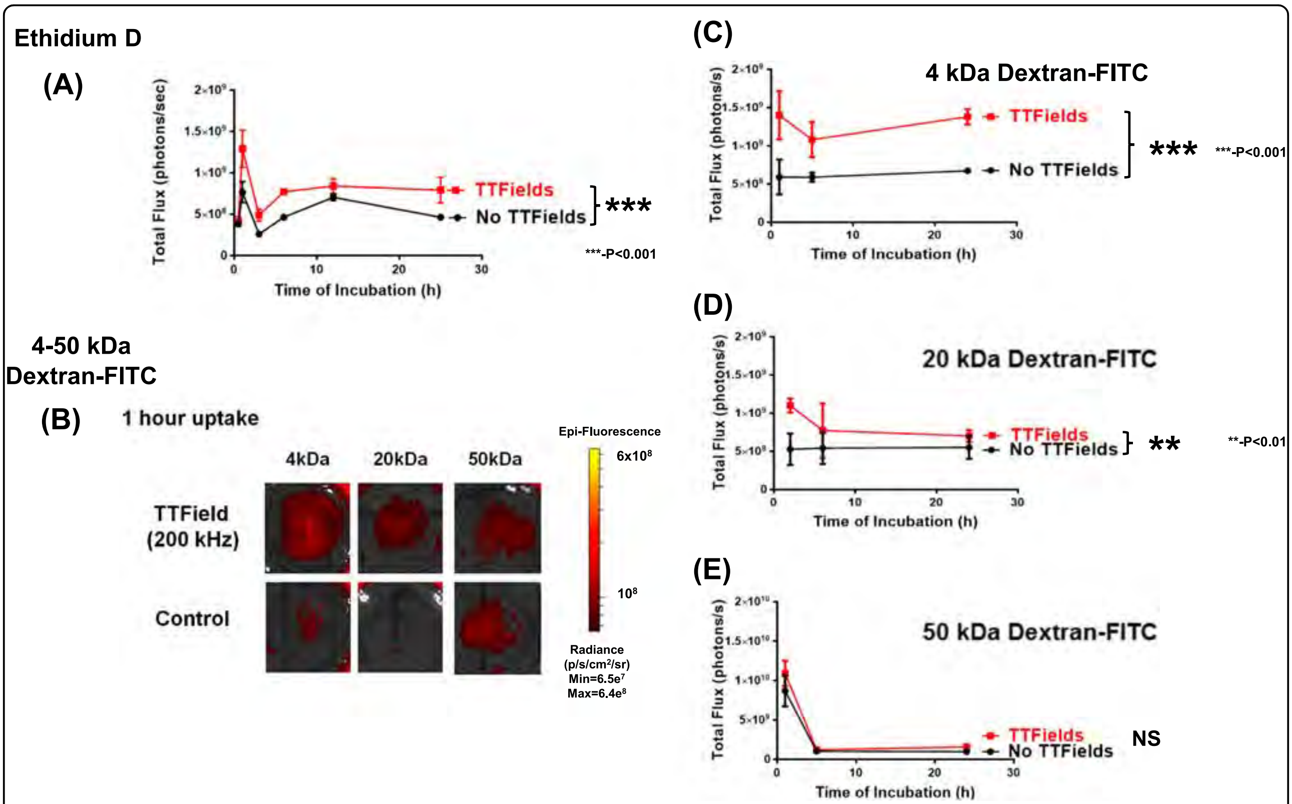

Fig. 3 a Increased uptake of Ethidium D in U87-MG cells treated with TTFields, compared to the no TTFields condition (***$p < 0.001$). The effect of TTFields on the binding and uptake of Dextran-FITC of varying molecular weights in U87-MG cells. **b** A representative panel of Dextran-FITC fluorescence at 1 h incubation for 4, 20, and 50 kDa Dextran-FITC. Fluorescence scale bar shown on right. Impact of TTFields on the time course of Dextran-FITC uptake, **c** 4 kDa Dextran-FITC (***$p < 0.001$), **d** 20 kDa Dextran-FITC (**$p < 0.01$), and **e** 50 kDa Dextran-FITC ($p = 0.26$, not significant), compared to that of no TTFields. All statistical comparisons were based upon 2-way ANOVA analyses with each data point represented by $n = 3$ experiments. APC, allophycocyanin, Ethidium D, ethidium bromide, FITC, fluorescein isothiocyanate

accumulated over time but the rate of fluorescence intensity increase was significantly augmented (Fig. 4c, d, $p < 0.001$, two-way ANOVA, TTFields vs. no TTFields) for TTFields-exposed co-cultures compared to TTFields-unexposed co-cultures. In a separate set of experiments, by 24 h of TTFields application, the ratio of PpIX fluorescence intensity in the U87-MG glioblastoma cells over the surrounding PCS-201 fibroblast cells was significantly increased (Supplemental Figure S8, $p = 0.043$, two-way ANOVA, TTFields vs. no TTFields).

SEM shows that TTFields alters membrane morphology of U87-MG/eGFP-fLuc cells

Figure 5a, b shows representative SEM images of low-density (5,000 cells/coverslip) U87-MG/eGFP-fLuc cells that were either not exposed to TTFields (Fig. 5a) or exposed to TTFields for 3 days (Fig. 5b). There was a significantly increased number of holes greater than 51.8 nm^2 in size (equivalent to 9 $pixels^2$ on 60,000× magnification) within the ROI of TTFields-exposed cells (53.5 ± 19.1) compared to the TTFields-unexposed cells (23.9 ± 11.0), ($p = 0.0002$, univariate Mann–Whitney test). Average size of the holes within the ROI was also significantly greater in TTFields-exposed cells (240.6 ± 91.7 nm^2) compared to TTFields-unexposed cells (129.8 ± 31.9 nm^2), (Fig. 5c, $p = 0.0005$ (univariate Mann–Whitney test)). In contrast to U87-MG cells, TTFields did not significantly alter the size nor the number of holes in normal human fibroblast cells (Fig. 6).

The effects of a 24-h exposure to TTFields on the plasma membranes of U87-MG cells seeded at high density are shown in Supplemental Figure S10. Topological alterations of the membrane surfaces are best seen with subpanels with the 2–4 µm scale bars. For no TTFields samples, the cell surface appeared to be covered in densely matted, elongated and flattened membrane extensions, similar to membrane ruffles and contiguous with the cellular membrane. In contrast, after 24 h of exposure to TTFields, the densely matted and elongated structures were replaced by short, bulbous and bleb-like structures. TTFields did not appear to alter the membrane morphology of normal human PCS-201 cells (data not shown).

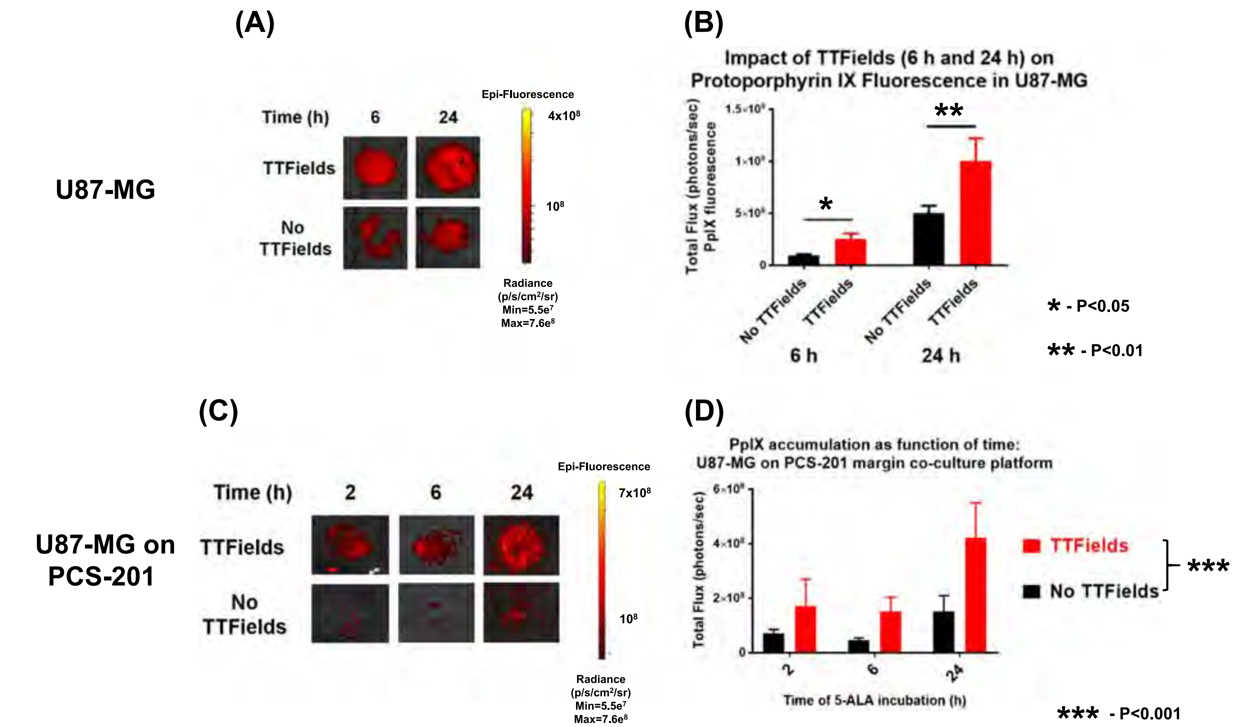

Fig. 4 Effect of TTFields on 5-aminolevulinic acid (5-ALA) uptake as shown. a representative protoporphyrin IX (PpIX) fluorescence panel for TTFields-unexposed vs. TTFields-exposed U87-MG cells after 6 and 24 h of exposure. Scale bar on right used for both 6 h and 12 h post-exposure data. **b** Quantitation of images in **a** showed significant increase in PpIX signals in TTFields exposed cells compared to no TTFields, at both 6 h ($p = 0.047$) and 24 h ($p = 0.01$) time points. All monovariant statistical comparisons between no TTFields vs. TTFields samples done by Student's *t*-test for $n = 3$ experiments per time point. **c**, **d** Effect of TTFields on U87-MG glioblastoma cells co-cultured with PCS-201 fibroblast cells. **c** Representative fluorescent panels of 5-ALA uptake (and subsequent PpIX fluorescence, Ex = 558 nm, Em = 583 nm) for no TTFields (top row) vs. TTFields (bottom row) conditions. Duration of exposures are 2, 6, and 24 h. **d** Quantification of time course of PpIX accumulation (and thus accumulation of fluorescent flux as expressed as photons/s) in the glioblastoma-fibroblast co-culture platform under TTFields exposed vs. unexposed conditions ($p < 0.001$). Statistical analyses consisted of two-way ANOVA for no TTFields vs. TTFields conditions, and $n = 3$ experiments per time point. Schematic of co-culture platform is shown in Supplemental Figure S4

The effect of TTFields on membrane permeability is reversible

To assess the reversibility of the effect of TTFields on cancer cells, U87-MG/eGFP-fLuc cells were subjected to three conditions: (1) No TTFields exposure, standard cell culture conditions (37 °C, 95% O_2, 5 %CO_2), (2) TTFields exposure (24 h) and (3) TTFields exposure (24 h) followed by no TTFields exposure (24 h). The readouts of BLI, PpIX fluorescence and Dextran-FITC fluorescence were acquired (Fig. 7 and Supplemental Figures S11-S15). The presence of TTFields (24 h) significantly increased BLI flux compared to no TTFields exposure (Fig. 7, $p < 0.0005$, two-way ANOVA, TTFields vs. no TTFields, Supplemental Figures S11) but this increase was significantly attenuated when the cells were re-introduced to the no TTFields condition for 24 h (Fig. 7, two-way ANOVA, $p < 0.005$, TTFields [24 h] vs. TTFields [24 h] followed by no TTFields [24 h]). A similar pattern of reversible readouts occurred with PpIX fluorescence (Supplemental Figure S12A, $p < 0.0005$, two-way ANOVA, TTFields vs. no TTFields and $p < 0.0004$, TTFields vs. TTFields followed by no TTFields) and for 4 kDa Dextran-FITC fluorescence (Figure 12B, $p < 0.05$, two-way ANOVA, TTFields vs. no TTFields; and $p < 0.05$, TTFields vs. TTFields followed by no TTFields). For each experimental set, eGFP fluorescence did not significantly change (Supplemental Figures S11 and S13). SEM investigations also revealed that the significant augmentation in both the number of holes (Supplemental Figure S16-S17, $p = 0.007$, two-way ANOVA, TTFields vs. No TTFields) and the size of holes (Supplemental Figure S17, $p = 0.0007$, two-way ANOVA, TTFields vs. No TTFields) by TTFields were reversible as well, after 24-h of no exposure.

Discussion

Previous studies have focused on the effects of TTFields on the nucleus (e.g., microtubules[39]), septin[14], mitochondria, and autophagy[16]. To our knowledge, this is the first study to report the effects of TTFields on cancer cellular membrane integrity. We confirmed the

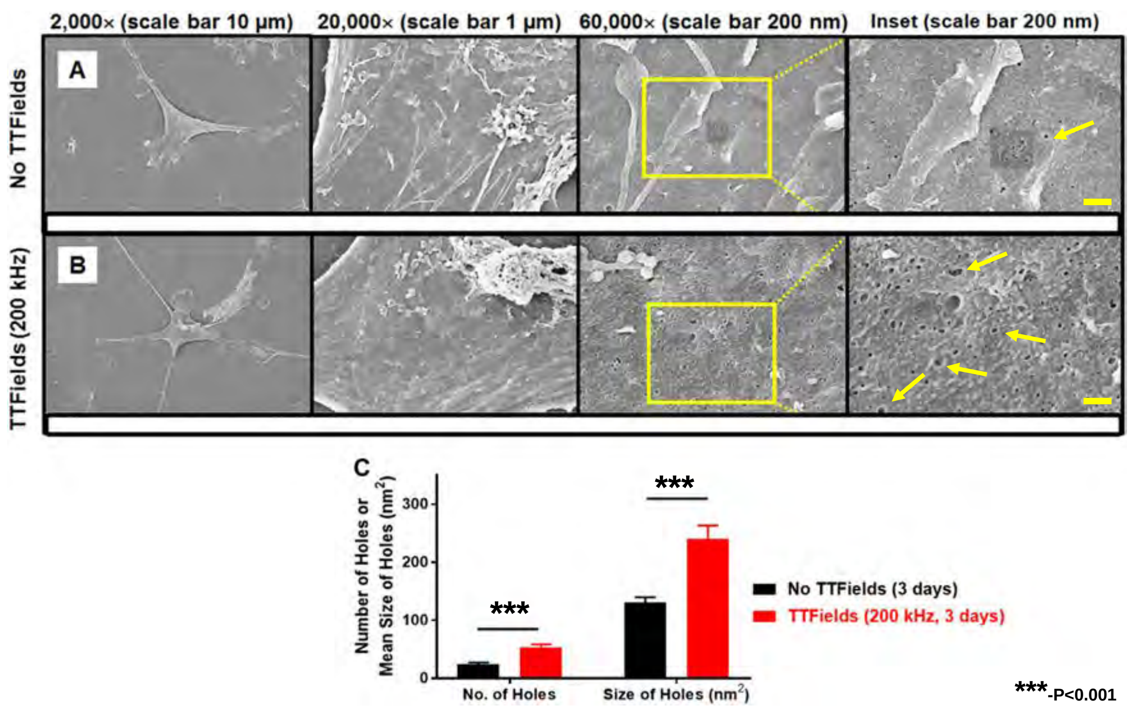

Fig. 5 Scanning electron micrograph (SEM) comparison of plasma membrane holes in glioblastoma cells unexposed or exposed to TTFields. a Representative SEM images of a U87-MG/eGFP-fLuc cell unexposed to TTFields for 3 days with sparse holes in the plasma membrane. **b** Representative SEM images of a U87-MG/eGFP-fLuc cell exposed to TTFields for 3 days demonstrate more holes and of larger size in the plasma membrane, compared to that of cells not exposed to TTFields (Wilcoxon rank-sum analysis). **c** Quantification and comparison between TTFields unexposed and exposed cells of the number and size of holes with area ≥ 51.8 nm^2 (equivalent to a 4-nm radius circle, or 9 pixels[2] on the 60,000× magnification images) within a 500 nm-radius circular region of interest. The minimum hole size cut-off was based on the 3.3 and 5.0 nm Stokes radii of 20 kDa and 50 kDa Dextran-FITCs, respectively. From left to right, magnification levels in **a** and **b** are 2,000× (black scale bar 10 µm), 20,000× (black scale bar 1 µm), and 60,000× (black scale bar 200 nm) and final panel column on the extreme right, where yellow scale bar represents 200 nm scale. Yellow arrows point to representative holes on cellular membranes. Coverslips from three experiments per condition were used, and at least 5 cells per coverslip were analyzed for hole count and size, in a double-blind manner. Qualitative comparison of changes to the plasma membrane in cells seeded at higher density for 24 h of TTFields exposure vs. no TTFields exposure is shown in Supplemental Figure S9

phenomenon of increased cellular membrane permeability for glioblastomas in the presence of TTFields across multiple human GBM cell lines. The readout employed to validate the hypothesis included bioluminescence imaging (Figs. 2, 7 and Supplemental Figures S2/S11), fluorescence imaging (Figs. 2, 3, 4 and Supplemental Figures S4/S7/S8/S13/S15), and scanning electron microscopy (Figs. 5, 6 and Supplemental Figures S10/S16/S17). Studies of TTFields in combination with chemotherapies have shown both therapeutic additivity[6,40,41] and synergy[18,42]. Future investigations should uncover why certain chemotherapies display additivity while other chemotherapeutics show synergy when combined with TTFields. For this study, we posited that TTFields mediates improved accessibility to cancer cells. Several experiments showed the reversibility of the TTFields effect on membranes thus demonstrating a causal relationship between TTFields and the increase in membrane permeability. Such observations also suggest that TTFields could be used to tune drug accessibility to cancer cells.

Our investigation into the cell permeability hypothesis of TTFields action was initiated partly because of our initial observation of increased bioluminescence in luciferase-expressing GBM cells by TTFields. We postulated that TTFields induced increased permeability in the cellular membranes of GBM cells. Increased GBM cell permeability to D-luciferin as measured by BLI was not due to the effects of TTFields on luciferase itself, but rather due to an increased influx of its substrate D-luciferin into the cells engineered to express the firefly luciferase. Furthermore, this finding held true for both ATP-dependent (FLuc) and ATP-independent luciferase (RLuc). Therefore, despite a preliminary report suggesting that intracellular ATP was increased in CT26 colorectal carcinoma cells exposed to TTFields[43], the observation of increased glioblastoma cell membrane permeability in the setting of TTFields exposure suggests an independent

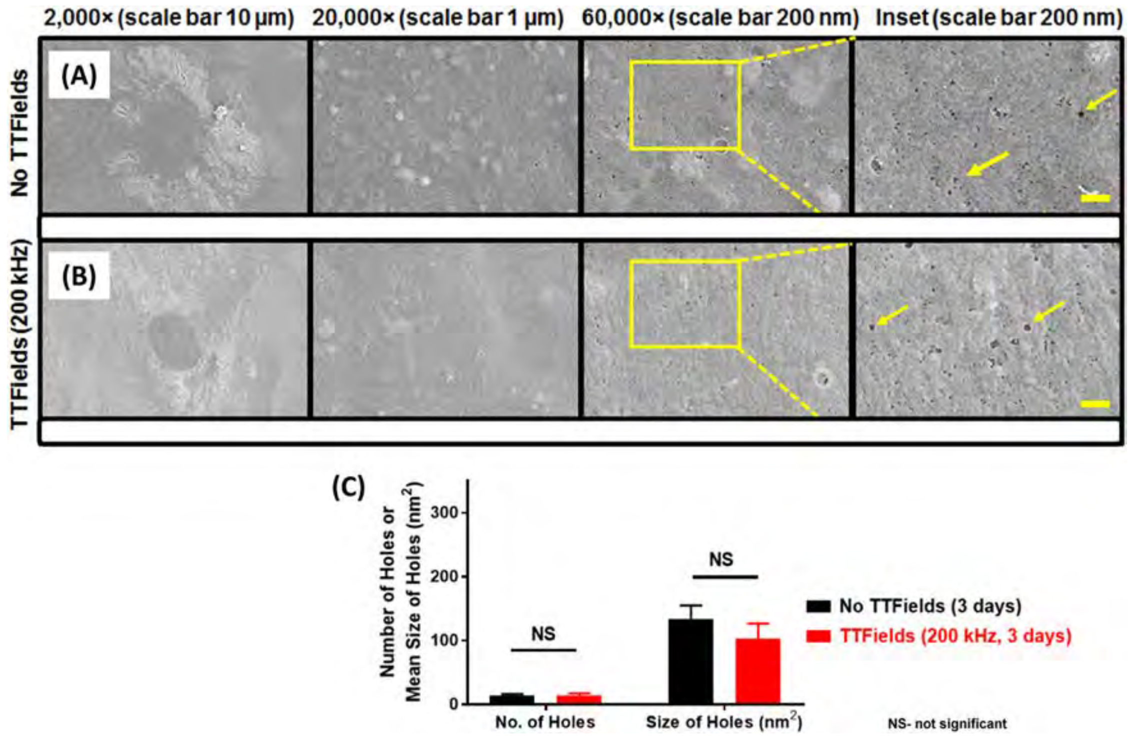

Fig. 6 Scanning electron micrographs (SEM) of normal human PCS-201 cells seeded at low density (5,000 cells per 13 mm glass coverslip, see Supplemental Figure S1). The cells were grown under standard tissue culture conditions (37 °C, 95% O_2, 5% CO_2). Non-TTFields-exposed cells (**a**) were left under those conditions for the duration of the study. Other cells (**b**) were exposed to TTFields for 72 h. **c** Quantification and comparison between TTFields unexposed and exposed cells of the number and size of holes with area ≥ 51.8 nm^2 (equivalent to a 4-nm radius circle, or 9 $pixels^2$ on the 60,000× magnification images) within a 500 nm-radius circular region of interest. The minimum hole size cut-off was based on the 3.3 nm and 5.0 nm Stokes radii of 20 kDa and 50 kDa Dextran-FITCs, respectively. There was no significant difference in the number or size of holes between the TTFields unexposed and exposed normal human PCS-201 cells (Wilcoxon rank-sum analysis). From left to right, magnification levels in **a** and **b** are 2,000× (black scale bar 10 μm), 20,000× (black scale bar 1 μm), and 60,000× (black scale bar 200 nm) and final panel column on the extreme right where yellow scale bar represents 200 nm scale. Yellow arrows point to representative holes on cellular membranes. Coverslips from three experiments per condition were used, and at least 5 cells per coverslip were analyzed for hole count and size, in a double-blind manner

phenomenon. An increased expression or activation of luciferase due to TTFields exposure could not have explained the increased BLI signal because in these cells the luciferase enzyme was controlled by the same promoter as was eGFP, and an increase in fluorescence signal was not observed in the same cells. However, exposure to TTFields may affect cellular metabolism that would be manifested by changes in ATP levels, alterations in membrane morphology and shifts in oxygen consumption.

Some key findings supporting the permeability hypothesis came from the Dextran-FITC validation experiments (Fig. 3b–e, Supplemental Figure S15). The accessibility of the cell membrane to small probes in the setting of TTFields was tested with FITC-labeled dextrans, which resulted in an increase in influx of 4 kDa (Stokes' radius ~1.4 nm[44]) and 20 kDa (Stokes' radius ~3.3 nm[44]) but not 50 kDa dextrans (Stokes' radius ~5 nm[44]). This suggests that TTFields cause GBM cells to become more permeant to substances as large as 20 kDa, but no greater than 50 kDa. For reference (Supplemental Table S1), the luciferin and coelenterazine substrates are of small enough molecular weight to be accessible through the membrane with TTFields exposure. D-luciferin (substrate for Firefly luciferase) has a molecular weight of 280.3 g/mol (~280 Da)[45], coelenterazine H (substrate for Renilla luciferase) has a molecular weight of 407.5 g/mol (~408 Da)[46],5-ALA has a molecular weight of 167.6 g/mol (169 Da), consistent with the Dextran-FITC findings.

Our SEM findings are reminiscent to those reported by Bouakaz[47]. We showed that at low seeding density, 3 days of TTFields exposure caused a significant increase in the number and size of holes greater than 51.8 nm^2 in area, compared to the no TTFields condition (Fig. 5). This hole size cut-off represents a circle of radius 4.1 nm, which is the Stokes' radius of a FITC-dextran molecule with a size of 20–40 kDa

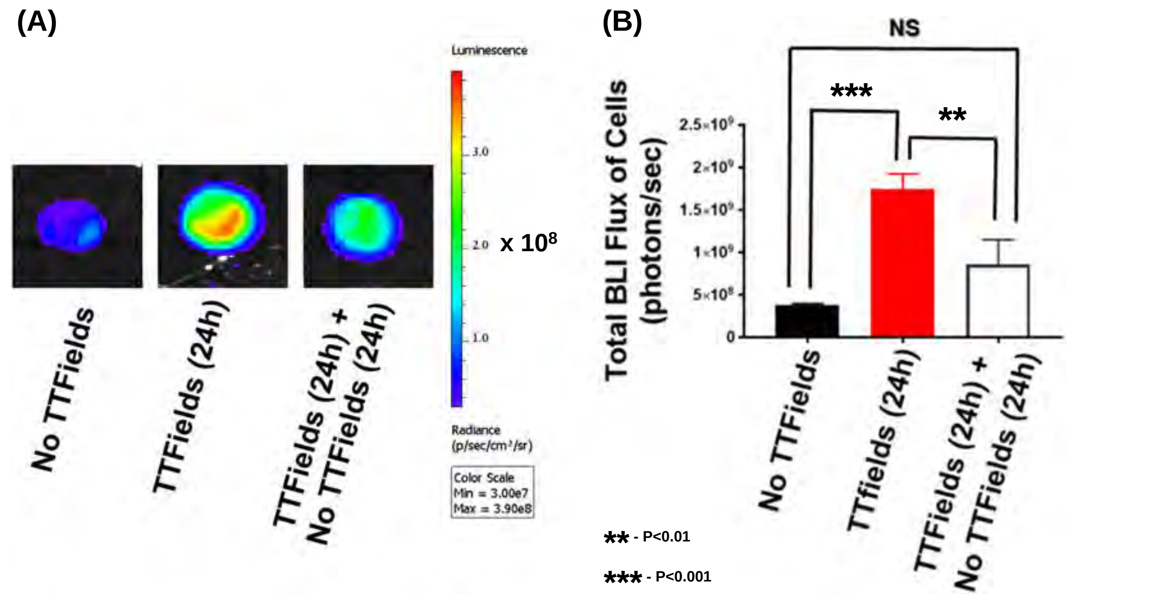

Fig. 7 Study showing the reversibility of TTFields' effects on bioluminescence activity of U87-MG/eGFP-fLuc cells. Cells were subjected to the conditions of: (1) standard, control tissue culture settings of 37°C, 95% O_2, 5% CO_2 and no exposure to TTFields, (2) 24 h of TTFields exposure, and (3) 24 h of TTFields exposure followed by additional 24 h of no TTFields exposure. All experimental conditions were done in triplicate and statistical analysis calculated via 2-way ANOVA. NS stands for not significant. **a** Representative panel of bioluminescent imaging (BLI) scans as a function of the three aforementioned conditions (i.e., no TTFields, TTFields (24 h), TTFields (24 h) followed by no TTFields (24 h)) and **b** quantification of BLI data in **a**. BLI, bioluminescent imaging, eGFP, enhanced green fluorescence protein, fLuc, firefly luciferase

(Supplemental Table S1). Thus, the difference in cell membrane disruption visualized by SEM confirms the indirect observations from our FITC-dextran studies. Interestingly, exposure of normal human fibroblasts (PCS-201) to TTFields caused no significant increase in the number or size of cellular membrane holes, thus suggesting that the permeability effect may have some specificity to cancer cells. Qualitatively, for U87-MG cells, there was a clear onset of bulbous, bleb-like structures due to a 24-h exposure to TTFields under high seeding density (Supplemental Figure S10). The appearance of these structures is consistent with increased permeability in the outer membrane[48] and the induction of apoptosis[49–51] although in our hands, there is little evidence of an apoptotic phenotype with a 24-h TTFields exposure. In our studies, high-density PCS-201 cells displayed no such changes with TTFields exposure (data not shown) thus suggesting again, the specificity of the TTFields effect for cancer cells.

Although we did not synchronize the cell cycle for our experiments, the doubling time of the U87-MG cells is ~48 h and given that, TTFields exert their maximal anti-proliferative effect on dividing cells, this could explain the lack of observed abundant apoptosis after a 24-h TTFields exposure. An alternative interpretation may lie in reports that cellular blebbing may confer resistance to cellular lysis[52]. A previous report in unsynchronized glioblastoma cells demonstrated that 72 h of TTFields exposure induced cell death with a marked proportion of Annexin V-positive cells[16]. Using transmission electron microscopy, they also showed signs of autophagy including autophagosomes, swollen mitochondria, and a dilated endoplasmatic reticulum[16]. In contrast, we used SEM to better visualize the effects of TTFields specifically on the plasma cell membrane.

The increase in membrane permeability by TTFields may have clinical implications. Using the co-culture platform of human GBM cells layered on top of normal human fibroblast cells, we studied the impact of TTFields on the uptake of 5-aminolevulinic acid (5-ALA) into GBM cells.[53] We showed that TTFields exposure resulted in significantly increased 5-ALA uptake in the GBM cells compared to the fibroblast cells[53]. In June 2017, 5-ALA was approved by the Food and Drug Administration for clinical use in the United States to assist neurosurgeons in delineating the tumor-normal brain border during glioma resection[54]. Future clinical studies may consider pre-treating glioma patients with TTFields prior to 5-ALA administration, possibly to enhance the delineation of the infiltrative tumor margin during tumor resection. In addition, the impact of TTFields on blood-brain permeability may warrant investigation.

With regard to detecting and measuring the effects of TTFields on cancer cells, the majority of cell culture-based studies to date have focused on cell count/viability as the primary readout[8,14,16,18,55]. This is based on the prevailing understanding that TTFields interferes with mitosis of rapidly dividing tumor cells, which results in cancer cell death. In addition, computational modeling studies of TTFields in cell culture are currently driven by cell count as the primary outcome of the model[11,56,57]. As additional mechanisms of action of TTFields (e.g., increase in cellular permeability described in the current study) emerge, additional read-outs based on these mechanisms will follow suit.

Recurrence of GBM is inevitable and the median time to first recurrence despite standard therapy is approximately 7 months[58,59]. In clinical applications of TTFields to patients with GBM, the data suggest that increased compliance and duration of TTFields use correlates with improved survival[60–62]. TTFields compliance (≥75% vs. <75%) was an independent predictor of overall survival in the retrospective analysis of the full EF-14 trial dataset[2] and the duration of use of TTFields was also found to affect overall survival[60]. Taken together, these data may serve as clinical correlates of the observed effects in the cell cultured-based TTFields experimental setting. Namely, we observed a correlation between the length of TTFields exposure and the duration of its effect on cell membrane permeability after cessation of TTFields. At lengths of TTFields exposure of 0.5–3 h, the duration in BLI augmentation (compared to no TTFields conditions) lasted about 5 min. However, at TTFields exposures of 12–25 h, this difference in BLI between TTFields and no TTFields conditions lasted for more than 20 min (Supplemental Figure S9A). Likewise, a re-analysis of the data reported by Ram et al.[60] shows that the percent increase in overall survival (in patients treated with TTFields plus temozolomide vs. temozolomide alone) jumped from 32% after 1 year of TTFields exposure to 551% after 5 years of TTFields exposure, respectively (Supplemental Figure S9B).

This study should be considered in the context of its limitations. We cannot confirm our results in an animal model of glioblastoma because a practical device that delivers TTFields to rodent brain does not yet exist. In addition, we focused our work in glioblastoma cells using the 200 kHz TTFields frequency, because currently FDA approval exists only for glioblastoma and only at this frequency. The novelty of the findings is the first report of a direct effect of TTFields on increasing, in a reversible manner, plasma membrane permeability in glioblastoma cells, which has clinical implications as described above. Nevertheless, we propose that our studies will influence future treatments of glioblastomas. Given the increasing interest in TTFields within the scientific and clinical literature, the future foreshadows additional insights into mechanisms of TTFields.

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Conflict of interest
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Case Report

CASE REPORT

The role of erlotinib and the Optune device in a patient with an epidermal growth factor receptor viii amplified glioblastoma

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Abstract

The standard treatment for patients diagnosed with glioblastoma is surgical resection of tumor followed by high dose radiation and chemotherapy with temozolomide. For patients who experience allergic reactions to temozolomide despite desensitization protocols, alternative therapies must be considered. In this report, we present such a patient who then received treatment with an epidermal growth factor receptor inhibitor, erlotinib, concurrent with a tumor-treating field device, Optune. Through this combination of a targeted molecular therapy and the Optune device, the patient has been able to achieve stable disease 9 months after completing radiation.

INTRODUCTION

Temozolomide (TMZ) is part of the standard chemotherapy regimen for patients with newly diagnosed glioblastomas (GBMs) [1]. If a patient experiences an allergic reaction to TMZ, a desensitization protocol is implemented [2]. If this fails, other chemotherapeutic agents must be considered. In this case report, a patient who was unable to sustain multiple cycles of TMZ is treated with an epidermal growth factor receptor (EGFR) inhibitor in combination with tumor-treating electric fields (TTFs) and has been able to achieve a stable disease course.

CASE REPORT

A 66-year-old woman presented with polyuria and polydipsia for 3 weeks prior to evaluation by her primary care physician. Because of the concern for diabetes insipidus, the patient underwent MRI of the brain with and without contrast. Scans showed a right temporoparietal brain lesion ~4.5 cm × 4 cm in size (Fig. 1). The patient underwent surgical resection, and the neurosurgeons achieved gross total resection with an absence of visible disease on contrast-enhanced MRI. A diagnosis of GBM was made and testing determined the tumor to be methyl

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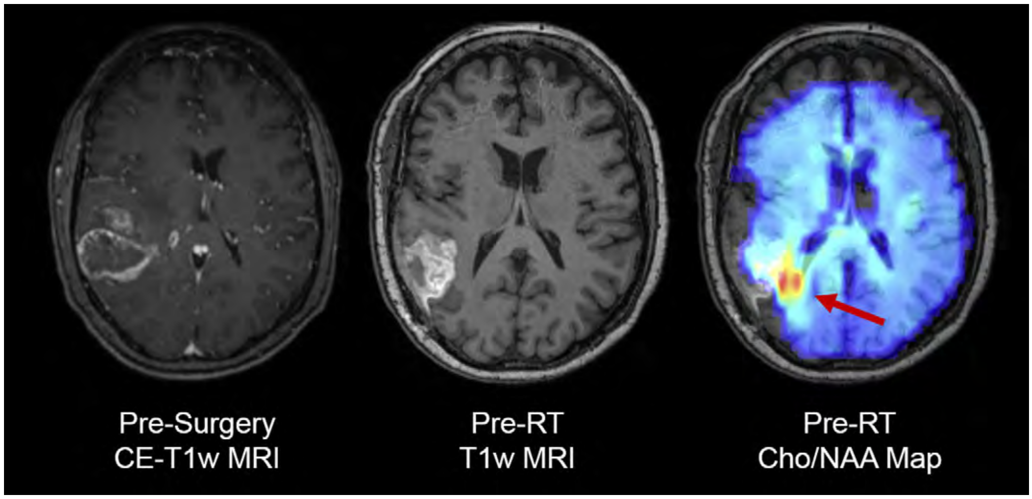

Figure 1: Contrast-enhanced T1-weighted MRI (CE-T1w MRI) indicated a high-grade brain tumor at the time of diagnosis, which was surgically resected and confirmed to be glioblastoma. Prior to starting chemoradiation, spectroscopic MRI showed an elevated choline to *N*-acetylaspartate (Cho/NAA) lesion medial to the resection cavity, indicating the presence of residual active tumor (red arrow)

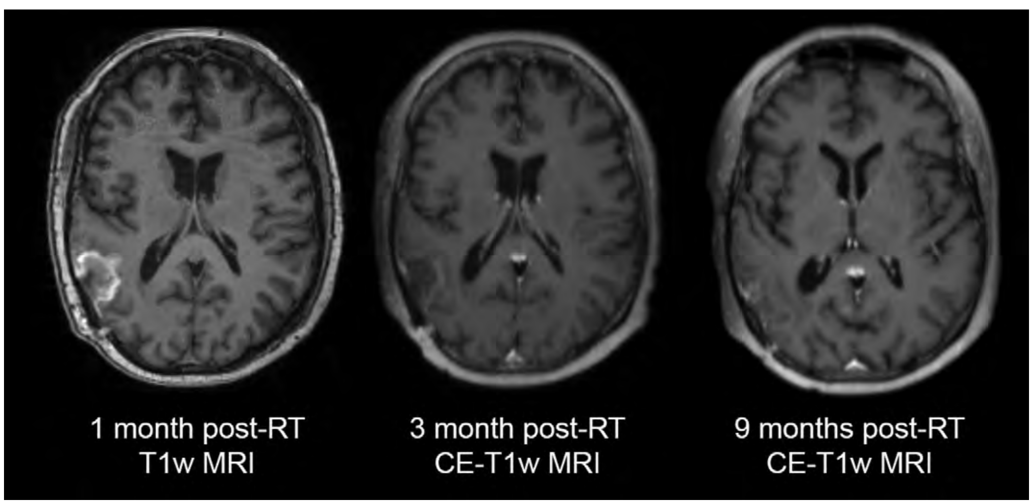

Figure 2: The patient's disease has been stable for a period of 9 months post-radiation therapy (RT) via maintenance therapy consisting of erlotinib + Optune after the patient was removed from the standard TMZ regimen due to a hypersensitivity reaction

guanine methyl transferase (MGMT) hypermethylated, *EGFR* amplified and EGFRviii positive.

The patient opted to enroll in a clinical trial that uses 3D spectroscopic MRI [3] to monitor the metabolic response of patients to an experimental histone deacetylase inhibitor (HDACi), belinostat, concurrent with TMZ and radiation therapy. Pan-isoform HDACi's like belinostat are hypothesized to have a synergistic effect with TMZ for radiosensitization of tumor cells; belinostat has more blood–brain barrier penetration than other HDACi's [4]. A post-resection sMRI scan suggested the presence of residual non-enhancing disease. She received 60 Gy radiation in 30 fractions over 6 weeks in conjunction with belinostat and TMZ, and appeared to have stable disease per MRI 1-month post-radiation (Fig. 2).

One month later, the patient experienced linguofacial swelling and hives after her first cycle of adjuvant TMZ. Recognizing this to be an allergic reaction, an extensive desensitization regimen was performed to no avail. The patient was taken off the clinical study and alternative chemotherapeutic agents were considered. Since the patient could not tolerate TMZ and refused to try other alkylating agents, and noting that her tumor exhibited mutated *EGFR*, she was started on erlotinib, an EGFR inhibitor used primarily in treatment of non-small cell lung cancer [5]. Concurrently, she began use of Novocure's Optune, a device which generates low intensity TTFs via a scalp-mounted transducer array [6]. The patient has tolerated the treatment well and her complaints thus far have been left arm paresthesia while playing stringed instruments, as well as scalp, face and arm irritation from the Optune device. She is on a regimen of 7× 150 mg tablets of oral erlotinib weekly. Per imaging and clinical course, she appears to have stable disease 9 months post-radiation (Fig. 2).

DISCUSSION

Standard of care for patients with GBM consists of maximal safe tumor resection followed by radiotherapy with concurrent and then adjuvant TMZ. Virtually all patients that receive this

multifaceted treatment regimen eventually experience disease progression, resulting in a median overall survival of only 16–19 months [1]. Recognizing the need for improved treatments for GBM, recent clinical trials have evaluated the efficacy of intermediate-frequency TTFs as an additional maintenance therapy [7]. In these clinical trials, overall survival was observed to improve by a median of 5 months when TTFs were included in combination with radiotherapy and TMZ. Although TTFs are now clinically employed as a component of GBM maintenance therapy along with TMZ, use of TTFs in combination with other molecularly targeted GBM therapies has yet to be evaluated. An assessment of such alternative therapeutic strategies is greatly needed for patients who are unable to tolerate the standard-of-care TMZ regimen, such as in the case of the patient presented in this report.

Recent efforts have been made to sequence the exomes of GBMs to identify prognostic markers and promising therapeutic targets. Two commonly recurring genetic lesions in GBM are amplification of *EGFR* and deletion of *EGFR* exons 2–7, which results in the generation of a constitutively active EGFRviii variant that drives tumor proliferation. Molecular profiling of this patient's tumor revealed both *EGFR* amplification and deletion of exons 2–7, indicating that her tumor may be driven by overactivation of *EGFR*-related cell signaling pathways. While clinical trials evaluating the efficacy of EGFR tyrosine kinase inhibitors (TKIs, e.g. erlotinhib) in the treatment of EGFR-driven GBM have demonstrated no overall patient survival benefit, potentially because of the poor CNS penetration of TKIs [8], recent studies have shown efficacy of anti-EGFR antibodies conjugated to cytotoxic drugs as a vehicle for EGFR-directed therapies [9].

To date, few studies have examined the combined use of TTFs and targeted molecular therapies in the maintenance therapy stage of GBM treatment. Here, we report the use of a targeted EGFR inhibitor, erlotinib, in combination with TTFs in the maintenance therapy of a patient's GBM tumor following maximal surgical resection. This therapeutic combination, initiated as an alternative therapy because of the patient's hypersensitivity to TMZ, has resulted in stable tumor size and disease course for 9 months following completion of radiotherapy. While the exact role of erlotinib in this patient's treatment outcome is unclear, prior surgical resection has resulted in significant blood–brain barrier disruption that allows for enhanced CNS uptake of therapeutic agents. It has also been hypothesized that TTFs may be able to further improve CNS penetrance of therapeutic agents [10], though this would need to be examined by future studies.

To our knowledge, this is the first report of combining erlotinib with the Optune device. We propose that further clinical trials that evaluate the use of targeted molecular therapies in combination with tumor-treating fields may be warranted, particularly for patients that are unable to tolerate standard TMZ chemotherapy.

FUNDING

This work was supported by the National Institutes of Health [U01CA172027].

CONFLICTS OF INTEREST STATEMENT

No conflicts of interest.

CONSENT

Written informed consent was obtained from the patient for this case report.

GUARANTOR

The last author of this study (S. Sengupta) guarantees for the accuracy of this case report.

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Tumour-treating fields complement glioblastoma treatment

The addition of tumour-treating fields to standard gioblastoma therapy improves progression-free survival (PFS) and does not negatively affect patients' health-related quality of life (HRQoL), according to recent findings.

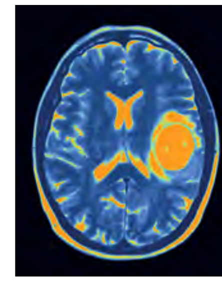
In the secondary analysis of the EF-14 phase 3 randomised trial, Martin Taphoorn (Haaglanden Medical Center, The Hague, Netherlands) and colleagues examined the association between tumour-treating fields therapy, HRQoL, and PFS in 695 patients with glioblastoma who had completed standard radiochemotherapy. Patients were randomly assigned (2:1) to receive temozolomide plus tumour-treating fields (n=466) or temozolomide alone (n=229). The primary endpoint (previously reported) was PFS, and HRQoL was a predefined secondary endpoint.

639 (92%) of the 695 enrolled patients completed the baseline HRQoL questionnaire. HRQoL—measured as deterioration-free survival and time to deterioration on nine preselected scales and items—did not differ between the treatment groups on most scales, except for itchy skin, which was worse with tumour-treating fields (median time to deterioration 8·2 months with tumour-treating fields *vs* 14·4 months with temozolomide alone; hazard ratio [HR] 1·85, 95% CI 1·33–2·57; p<0·001), and pain, which was improved with tumour-treating fields (13·4 *vs* 12·1 months, respectively; HR 0·65, 0·48–0·89; p<0·001). Deterioration-free survival was significantly longer in patients who received tumour-treating fields than in those on temozolomide alone, in terms of global health status, physical and emotional functioning, pain, and leg weakness (all p<0·01)—probably attributable to the improved PFS in this treatment group.

"This secondary analysis ... shows that the addition of tumour-treating fields to standard therapy for glioblastoma patients results in prolonged survival, without a negative impact on patients' health-related quality of life, except for more itchy skin," said Taphoorn. "The extension of (progression-free) survival is meaningful for patients, as their functioning and wellbeing is maintained during stable disease."

"This analysis showed that a variety of HRQoL measures favoured newly diagnosed glioblastoma patients treated with tumour-treating fields and temozolomide," added Eric Wong (Harvard Medical School, Boston, MA, USA). "This HRQoL and the final analyses of the randomised trial represent a tour de force quest by forward-thinking neuro-oncologists for effective therapies for glioblastoma."

Elizabeth Gourd



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For the **study by Taphoorn and colleagues** see *JAMA Oncol* 2018; published online Feb 1. DOI:10.1001/jamaoncol.2017.5082

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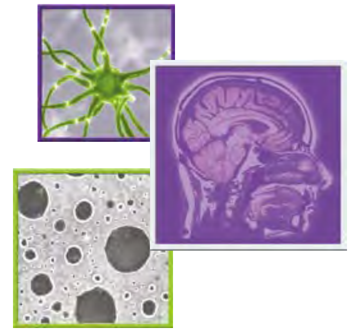

Estimated lifetime survival benefit of tumor treating fields and temozolomide for newly diagnosed glioblastoma patients

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Practice points

- Tumor treating fields (TTFields) for glioblastoma resulted in 5-year survival of 12.8% in the EF-14 trial.
- Epidemiological data suggest glioblastoma survival prognosis improves with time.
- We combined trial and epidemiological data to model lifetime glioblastoma survival.
- Modelling indicates a substantial increase in lifetime survival for GBM patients treated with TTFields.

Aim: To estimate the mean lifetime survival benefit, an essential component of health economic evaluations in oncology, of adding tumor treating fields (TTFields) to maintenance temozolomide (TMZ) for newly diagnosed glioblastoma patients. **Methods:** We integrated EF-14 trial data with glioblastoma epidemiology data. The model provided for an evidence-based approach to estimate lifetime survival for the material number of EF-14 trial patients still alive at 5 years. **Results & conclusion:** Patients treated with TTFields and TMZ had an incremental mean lifetime survival of 1.8 years (TTFields/TMZ: 4.2 vs TMZ alone: 2.4). Patients alive at year 2 after starting TTFields had a 20.7% probability of surviving to year 10. The results presented here provide the required incremental survival benefit necessary for a future assessment of the incremental cost–effectiveness of TTFields.

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Keywords: conditional survival • glioblastoma • life years gained • long-term survival • survival model • tumor treating fields

Glioblastoma (GBM) is the most common and aggressive primary brain malignancy. The estimated incidence of GBM is 12,390 new cases each year in the USA [1]. The age at diagnosis is in the mid-60s in epidemiology reports and in the mid-50s in clinical trial populations [2–4]. The disease progresses rapidly without advanced treatment; however, clinical and epidemiological literature has consistently indicated that a small subset of patients survives to 5, 10 and 15 years [5–7].

Tumor treating fields (TTFields) are low-intensity alternating electric fields delivered at intermediate frequencies intended to disrupt cancer cell division and inhibit tumor growth. TTFields have been studied since the year 2000 in preclinical models and in-clinical trials for GBM and other solid tumor cancers [8,9]. The therapy is delivered to GBM patients by transducer arrays placed on the scalp. TTFields rely on a novel physics-based mechanism of action that is unlike previous applications of electricity or ionizing radiation in medicine [10].

The US FDA approved TTFields as a GBM treatment initially in 2011 for recurrent GBM and later in 2015 for newly diagnosed GBM [8], based on the interim results of the randomized, controlled Phase III EF-14 trial. The final analysis of the EF-14 trial demonstrated that adding TTFields to maintenance temozolomide (TMZ) chemotherapy within the existing standard of care significantly prolonged median overall survival compared with the standard of care alone (20.9 vs 16.0 months; HR: 0.63; $p < 0.00006$) [11]. The combination of TMZ and TTFields has resulted in the first report from a large clinical trial of 5-year survival in GBM greater than 10% [11].

Future Medicine

Table 1. EF-14 survival rates.

Survival	TTFields with maintenance TMZ (%)	Maintenance TMZ alone (%)
Year 1 survival	73.2	65.3
Year 2 survival	43.1	30.7
Year 3 survival	25.9	16.3
Year 4 survival	19.6	7.9
Year 5 survival	12.8	4.5

TMZ: Maintenance temozolomide; TTFields: Tumor treating fields.
Data taken from [11].

The survival benefit was achieved without an increase in systemic toxicity or a decrease in quality of life [12]. The clinical use of TTFields is increasing and the therapy is now available in the USA, Germany, Austria, Switzerland, Israel and Japan [13]. The National Comprehensive Cancer Network has added TTFields as a standard-of-care treatment for GBM with a category 1 recommendation based on the EF-14 trial results [14].

An understanding of the predicted prognosis for GBM patients after the clinical trial period is important to facilitate informed clinical, personal and policy decision-making. Specifically, healthcare payers and policymakers often benefit from evaluating the lifetime cost of a therapy against the lifetime clinical benefit. Clinical trials only report data for a specific time period, which is typically a maximum of 5 years in oncology. Healthcare payers require tools to model the expected future costs and survival times for those patients alive at the last reported date of a trial.

The challenge of modeling long-term GBM survival is that the disease is characterized by a period of high mortality after onset, followed by survival probabilities that increase with time from diagnosis [6,15]. Statistical survival extrapolations that are commonly used in outcomes research are based on regression analysis. These parametric distribution models rely on regression analysis of patient level clinical trial data and therefore do not allow for an assumption of a nonconstant hazard function with time from diagnosis [16,17].

Regression-based estimation methods are biased by the initial period of high mortality in GBM and will fail to account for the known presence of long-term survivors in GBM after clinical trial reported outcomes. Notably, there is evidence of TTFields-treated GBM patients surviving to 5 and 10 years after treatment, including after an initial progression of the disease [18–21]. These reported outcomes are consistent with epidemiological reports of long-term GBM survivors [6,22,23].

The objective of this study was to develop a model to estimate GBM survival that integrates clinical trial data with real-world reported outcomes for GBM populations. The model benefited from the availability of 5-year survival data of the EF-14 trial and multiple epidemiological studies of long-term survival outcomes in GBM.

Materials & methods

Integrated survival model approach

A Bayesian area under the curve survival model framework was constructed to estimate the overall life expectancy of newly diagnosed GBM patients. The incremental mean survival benefit was calculated as the difference between the two survival curves ($AUC_{incremental} = AUC_{TTF+TMZ} - AUC_{TMZ}$). The model was programed to represent a lifetime horizon, modeling patients from the start of TTFields with maintenance TMZ versus maintenance TMZ alone. Patients were assumed to start treatment at the age of 56 years, consistent with the EF-14 trial population. Survival was estimated over the next 40 years.

The model estimated both mean life years and conditional survival probabilities for long-term survivors. Conditional survival is defined as the probability of a patient surviving for y additional years given that they had already survived to x years from starting treatment or diagnosis [24].

The integrated survival model was designed to replicate the EF-14 trial design and population. The EF-14 trial enrolled 695 patients with GBM who had undergone maximal safe surgery, including biopsy only when surgery was not possible and completed 60 Gy of radiation with concurrent TMZ without tumor progression. Patients were randomized 2:1 to receive either TTFields with maintenance TMZ or maintenance TMZ alone.

The EF-14 Kaplan–Meier (K–M) survival data by year is reported for each arm in Table 1 and is based on the published final analysis of the trial data reported in 2017 [11]. The reported 5-year survival was 12.8% for patients treated with TTFields and maintenance TMZ versus 4.5% for patients treated with maintenance TMZ

alone (p = 0.004). The hazard ratio between the two arms was 0.63 (95% confidence interval [CI] 0.53–0.76; p = 0.00006). The K–M survival curves demonstrated that the benefit of adding TTFields was maintained throughout the entire 5-year trial period [11]. A subgroup or responder-based survival model was beyond the scope of this analysis and was not considered meaningful as the benefit of TTFields was not restricted to a specific group of patients [11].

The integrated survival model then synthesized the EF-14 K–M survival data from treatment initiation until year 5 with epidemiological survival rates in GBM from year 5 to year 15. Patients alive at year 15 are assumed to return to the baseline mortality rate of the age-adjusted US population [25].

The survival results were calculated with and without a 3% discount rate applied to future health outcomes. The use of a discount rate is common in health outcome and health economic studies, representing the theoretical higher value of near-term versus long-term survival and the 3% rate was selected based on current guidelines for US studies [26]. One-way and probabilistic sensitivity analyses were performed to assess uncertainty. Bayesian 95% credible ranges (CR) were estimated for each model outcome.

Selection of epidemiology data

The epidemiological data was selected based on a literature search. The MEDLINE® database of the US National Library of Medicine was accessed via the PubMed® website. A Boolean word search was conducted using the keyword combination 'glioblastoma' and 'long-term survival' or 'conditional survival'. Of the 473 publications screened, 22 publications were reviewed in full text and five publications were selected for a detailed review.

All five publications indicated that the probability of surviving GBM increased as patients survived longer from diagnosis and that the first 2 years after diagnosis were the period of the highest mortality hazard rates [6,15]. Two publications based on single institution reports were then excluded in favor of larger epidemiological populations [15,27].

The review of the three epidemiological studies identified the introduction of TMZ in 2005 to be a potential confounding factor [6,28,29]. TMZ became the principal chemotherapy used to treat GBM in 2005 after demonstrating a significant survival benefit both in median survival and 5-year survival [4].

Epidemiological reports that included pre- and post-2005 populations were subject to data censoring requirements that may have biased the reporting of the conditional survival rate from 5 years to 10 years after diagnosis. Specifically, the benefit of TMZ was available for analysis at the 5-year survival point but only patients from the pre-TMZ era were available for analysis at the 10-year survival mark.

The epidemiological data published by Porter *et al.* was selected for inclusion in the survival model based on its homogeneous population of patients who were treated prior to the introduction of TMZ. Porter *et al.* reported primary malignant and nonmalignant brain tumor cases diagnosed from 1985–2005 from the National Cancer Institute Surveillance, Epidemiology and End Results Program registries, including 5991 GBM patients. This study provided survival probabilities through 15 years after diagnosis with GBM. The probability of surviving GBM to 10 years and 15 years given survival to 5 years and 10 years was 70.4% (95% CI: 55.6–81.2%) and 84.0% (95% CI: 38.9–96.8), respectively [6].

The model utilized weekly cycles to calculate survival and converted the long-term conditional survival probabilities to weekly mortality probabilities. The 70.4% probability of surviving at year 10 given survival to year 5 was converted to a weekly survival probability of 0.9987 and inversely a weekly mortality probability of 0.0013. To test the sensitivity of the survival results to the accuracy of the epidemiological data utilized in this study, we varied the reported long term survival rates by ±20% for the period following year 5.

Additional parametric modeling

Parametric distribution models, including exponential, Weibull, log-logistic, and log-normal functions, of the EF-14 trial K–M survival data were developed for validity testing against the available reported real-world outcomes for long-term survival. This approach to test regression-based parametric models was previously reported by Holland *et al.* [30]. The parametric models were also developed to allow for use in probabilistic sensitivity analysis. The best parametric fit was assessed using a combination of Akaike's information criterion and face validity inspection for the 5-year trial data period.

Table 2. The conditional survival rates estimated by the integrated survival model.

Survival to year given 2-year survival	TTFields with maintenance TMZ	Maintenance TMZ alone
Year 2	100%	100%
Year 3	59.6%	53.1%
Year 4	45.3%	25.7%
Year 5	29.4%	14.7%
Year 10	20.7%	10.3%
Year 15	17.4%	8.7%

The conditional survival rates estimated by the integrated survival model at future time points given a patient has survived to 2 years.
TMZ: Maintenance temozolomide; TTFields: Tumor treating fields.

Table 3. Akaike information criterion scores.

Distribution	TTFields with maintenance TMZ	Maintenance TMZ alone
Exponential	5335.59	5392.48
Weibull	5286.62	5319.66
Log-Normal	**5227.00**	5332.34
Log-Logistic	5227.56	**5306.78**

AIC scores for parametric fits to EF-14 trial Kaplan–Meier overall survival data. Best fits (lowest scores) are bolded.
AIC: Akaike information criterion; TMZ: Maintenance temozolomide; TTFields: Tumor treating fields.

Results

Mean lifetime survival estimated by the integrated survival model

Survival benefits were estimated over a lifetime horizon and represent the mean survival accrued for a population of newly diagnosed GBM patients treated with and without adding TTFields to maintenance TMZ. The estimated mean lifetime survival was 4.2 years (95% CR: 3.8–4.6) when TTFields was added to maintenance TMZ and 2.4 years (95% CR: 2.3–2.6) for patients treated with maintenance TMZ alone, accounting for 1.8 incremental life years gained (LYG; 95% CR: 1.5–2.1). The resulting estimate of LYGs was 1.2 years after applying a 3% discount rate (95% CR: 1.1–1.4).

To test the sensitivity of the results to the epidemiology data utilized in this study, one-way sensitivity analysis varied the long-term survival rates reported by Porter *et al.* by 20%. Decreasing the epidemiology survival rates by 20% estimated a mean survival benefit of 1.4 years (undiscounted). Increasing the epidemiology survival rates by 20% resulted in an estimated survival benefit of 2.2 years (undiscounted).

Conditional survival estimated by the integrated survival model

The conditional probability for patients alive 2 years after starting treatment to survive to years 3, 4, 5, 10 and 15 are presented in Table 2. Patients treated with TTFields and maintenance TMZ who were alive at year 2 after starting treatment had a 29.4% probability of surviving to year 5 (95% CR: 24.4–31.2%) and a 20.7% probability of surviving to year 10 (95% CR: 14.0–24.6%). For patients treated with maintenance TMZ alone, the probability of surviving from year 2 to year 5 was 14.7% (95% CR: 18.5–23.7%) and the probability of surviving from year 2 to year 10 was 10.3% (95% CR: 11.2–18.3%).

Outcomes of regression-based parametric modeling and validity testing

The best fit for the TTFields with maintenance TMZ arm was the log-normal distribution and the best fit for the maintenance TMZ alone arm was the log-logistic distribution (Table 3). Despite being the best fit, the parametric curve for the maintenance TMZ alone arm visibly underestimated the EF-14 K–M survival results when plotted.

The parametric models also estimated conditional survival from year 5 to year 10 of 21.9% and 24.0% for treatment with TTFields and maintenance TMZ versus maintenance TMZ alone, respectively (Table 4). These results substantially underestimated survival compared with real world outcomes reported in large epidemiological studies [6,15,27–30].

Table 4. Comparison of parametric-estimated conditional survival rates to real-world reported outcomes in glioblastoma.

Conditional probability of survival for each 5-year interval	Parametric model: TTFields with maintenance TMZ (%)	Parametric model, maintenance TMZ alone (%)	Survival rates prior to TMZ (Porter *et al.*) (%)
Year 5 to year 10	21.9	24.0	70.4
Year 10 to year 15	32.4	42.7	84.0
Year 15 to year 20	40.5	54.8	N/A

TMZ: Maintenance temozolomide; TTFields: Tumor treating fields.

Discussion

GBM is a highly aggressive tumor that requires intensive treatment to maximize survival. The disease affects a relatively young population, indicating that the disease often strikes during the peak productive years for adults. The age of the patients also indicates that successful intervention has the potential to produce substantial survival benefits for those who survive the early stages of the disease when measured over the remaining lifetime of the patients.

The integrated survival model allows for the synthesis of 5-year survival data from a large randomized controlled trial and real-world outcomes for GBM patients alive 5 to 15 years after diagnosis. This integrated modeling approach relied on actual reported outcomes to estimate future survival and did not rely on statistical extrapolations and assumptions.

Regression-based parametric models produced survival estimates that were inconsistent with both the EF-14 trial data and epidemiological data. The parametric models estimated survival rates after year 5 that were substantially below the real-world outcomes reported by Porter *et al.* Additionally, the parametric models estimated a higher hazard of death after year 5 for patients treated with TTFields and maintenance TMZ than for patients treated with maintenance TMZ alone; a finding that was inconsistent with the EF-14 K–M survival data, which reported lower mortality rates for TTFields treated patients during the entire trial period [11]. The reason for this discrepancy is the constant hazard function for death overtime that is inherent to regression-based statistical parametric models was not observed in the EF-14 trial or previous analysis of GBM survival data [11,15].

The limitations of statistical extrapolation of GBM survival can be observed in the only prior attempt to model lifetime survival based on the EF-14 trial data, which estimated GBM survival using exponential extrapolation of median EF-14 survival rates [31]. We plotted the exponential extrapolation method against the reported EF-14 K–M survival curves in Figure 1. The exponential extrapolation had the worst fit by Akaike's information criterion testing (Table 3) and was a poor visual fit to the EF-14 K–M survival curves in Figure 1. Specifically, estimated 5-year survival for patients treated with TTFields and maintenance TMZ was only 5.5%, substantially below the actual reported K–M result of 12.8%.

The National Institute for Health and Care Excellence in the UK considered a similar survival model structure in its decision to license ipilimumab [32,33]. Recent academic research has also relied on this approach to assess ipilimumab and pembrolizumab [34,35].

The integrated survival model is subject to certain limitations. First, the model relied on trial and epidemiological survival rates as an input. The model therefore combined data from two sources and assumed that patients alive at 5 years in one dataset will have the same future outcomes as patients in the other dataset. The benefit of this approach is that long-term survival is consistent with available data from real-world reported outcomes over decades. The sensitivity analysis demonstrated that even if the modeled survival rate after year 5 was overstated by 20%, the incremental mean lifetime survival benefit of adding TTFields to maintenance TMZ was still substantial at 1.4 years.

Another limitation of the model is that the clinical trial input to the model was a single pivotal trial of TTFields. GBM is a relatively rare disease and multiple pivotal trials are generally not feasible prior to regulatory approval and product launch. The limitation is mitigated by the size and rigor of the EF-14 trial. The EF-14 trial was a multinational randomized controlled trial run in leading cancer institutions specialized in treating CNS tumors and enrolled 695 patients (about 5% of the GBM annual incidence in the USA). This risk is further mitigated by the fact that the survival results for the maintenance TMZ alone arm in the EF-14 trial were consistent with outcomes reported in a prior trial with a comparable design [36].

One more possible limitation of this model is that it does not differentiate between patients with different genetic tumor markers (e.g., *MGMT* promotor methylation and *IDH1* mutation). Patients with methylated

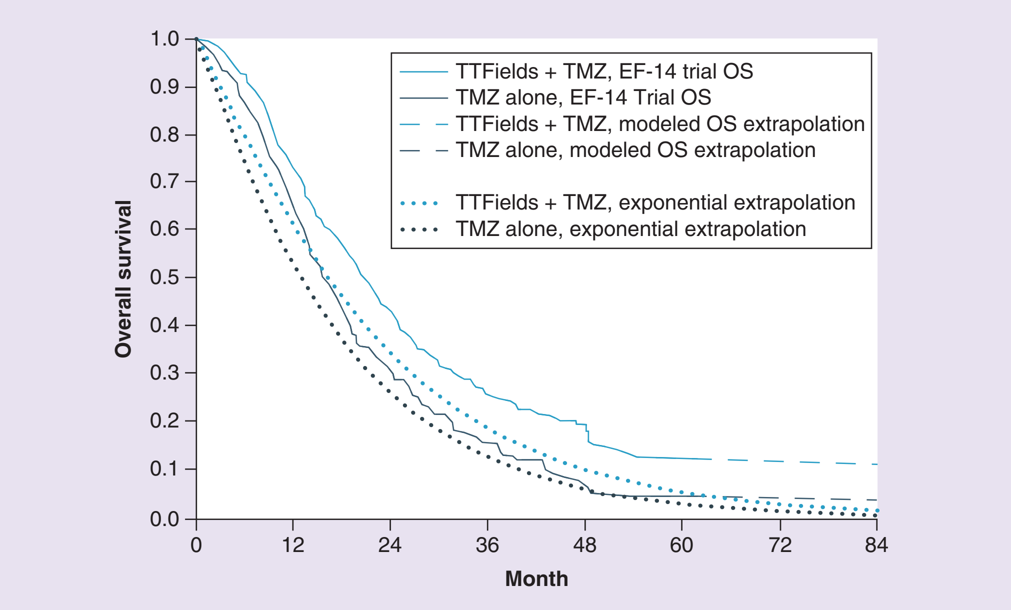

Figure 1. Comparison of final EF-14 survival curves (with modeled extrapolation) to the previously reported survival estimates.
OS: Overall survival; TMZ: Temozolomide; TTFields: Tumor treating fields.

MGMT promotors (about 40% of GBM patients) are known to have much longer survival times when receiving TMZ than those with unmethylated promotors [4,7]. In addition, patients with secondary GBM transforming from low-grade astrocytomas to GBM are characterized by mutated *IDH1* (about 6% of the GBM population). These patients have significantly longer survival times as well regardless of treatment. Although patients with these different genetic tumor markers were equally distributed between groups in the EF-14 trial, it is unknown whether the incidence of the different genetic markers is the same between the EF-14 trial and the epidemiological data used in this model, since Porter *et al.* did not report this data.

Conclusion

The integrated survival model provides physicians, patients and payers with the ability to estimate mean lifetime survival in GBM based on the synthesis of the most recent clinical data and epidemiological sources. This approach avoids the limitations of parametric survival models that are based on regression-analysis of patient level trial results. The integrated survival model results indicated that the addition of TTFields to maintenance TMZ resulted in a substantial increase in mean lifetime survival for GBM patients. This estimated increase in mean lifetime survival of 1.8 years is highly significant for a disease with an historical median survival of just over a year.

Availability of data & materials

All data generated or analyzed during this study are included in this published article.

Financial & competing interests disclosure

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Authors' contributions

G Guzauskas and B Wang contributed to conceptualization, methodology, formal analysis, original draft and reviewing and editing. M Salzberg contributed to supervision, validation and reviewing and editing.

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Invited Commentary

Tumor-Treating Fields
Answering the Concern About Quality of Life

Lia M. Halasz, MD; Timur Mitin, MD, PhD

Since the 2005 publication of the randomized European Organization for Research and Treatment of Cancer/National Cancer Institute of Cancer trial that established concurrent radiotherapy (RT) and temozolomide for upfront treatment of glioblastoma (GBM),[1] little progress has been made. Thus, it was remarkable when the interim results for the EF-14 trial were published, documenting a 4.9-month increase in median overall survival with the addition of tumor-treating fields (TTFields) to standard therapy with combined RT and temozolomide.[2] These findings were strengthened by presentation of the mature analysis at the Society for Neuro-oncology Meeting in 2016, which confirmed that the median survival improved from 16 months after randomization to RT plus temozolomide to 21 months with the addition of TTFields to RT plus temozolomide.[3] The survival advantage continued at later times, such as the 2-year survival rate of 30% vs 42.5% (P = .001).

Related article

Since its introduction, many physicians have remained skeptical about including TTFields as standard of care,[4] in part due to the novelty of the mechanism of action. The device generates low-intensity, intermediate-frequency (200 kHz) alternating electric fields that interfere with mitosis and disrupt the division of cells. Since its initial use for treatment of GBM, TTFields is now being tested for other cancer types, including metastatic non-small cell lung cancer,[5] and as an alternative to prophylactic cranial irradiation in small cell lung cancer (Oregon Health Sciences University/University of Washington trial, starting accrual in early 2018). Furthermore, physicians and patients have been concerned about the quality-of-life implications of wearing a mobile electrical device with 4 arrays of transducers continuously fixed to a shaved scalp for at least 18 hours a day. The battery pack for the device is large and heavy enough that it could interfere with daily activities. Quality of life remains a priority for many of our patients since clinical trials have shown incremental improvement in overall survival, but not cure.

An interim analysis of the EF-14 trial focusing on health-related quality of life (HRQoL), published by Zhu and colleagues,[6] suggested initial improvement in global HRQoL with TTFields in the first 6 months. Skin toxic effects concerns were higher among patients randomized to the combined TTFields, RT, temozolomide arm. The final analysis of these data, published by Taphoorn and colleagues[7] in this issue of *JAMA Oncology*, presents important data for evaluating the overall effect of TTFields on our patients. In contrast to the interim report, the investigators found no significant difference in HRQoL between the 2 treatment arms, except for itchy skin, which was worse with TTFields.

The finding of worsening itchy skin was not surprising given the known dermatologic adverse effects of the treatment. In the EF-14 trial, where TTFields was used with concurrent temozolomide shortly after RT, the rate of grade 1 and 2 skin toxic effects was 43%.[3] Because TTFields therapy is frequently being combined in the real-world setting with other agents, such as bevacizumab, the resultant skin toxic effects are not well studied and the incidence may be even higher. Hence, evaluation and appropriate and rapid management of skin toxic effects are critical to avoid significant treatment interruptions—and even discontinuation—to maximize TTFields therapy adherence and the resulting survival benefit.

One of the difficulties of this study,[7] which is common to many evaluations of HRQoL, is the low adherence to HRQoL assessments. Although 91.9% of patients had HRQoL assessments at baseline (before randomization), only 65.8% had assessments at 3 months and 41.7% at 12 months of follow-up. However, the authors performed sensitivity analyses with mixed-model analyses to account for missing data, which confirm their findings.

It is comforting to learn that the burden of carrying the device was not detrimental to patients' physical, social, or emotional functioning; however, overall it is important to remember that the trial participants were a highly selective group of patients. These individuals elected to take part in the trial, and thus represent a group of patients who are already open to wearing a device on their scalp daily for an indefinite time. In our experience, there are many social and cultural reasons that patients have for declining TTFields despite the data of improved survival. Many do not want the physical and visual cues that may remind them of their life-altering, life-limiting diagnosis. This factor may echo studies finding that patients with breast cancer rate alopecia as one of the most distressing treatment-related adverse effects because it can result in anxiety, depression, negative body image, lowered self-esteem, and reduced sense of well-being.[8]

With societal changes and the greater acceptability of wearable devices, ranging from fitness trackers to assistive technology, it will be interesting to see if patients become more open to utilizing TTFields. Moreover, whereas the patients participants in the EF-14 trial were using the first-generation TTFields system, weighing 2.7 kg, the currently used device weighs only 1.2 kg, which may lead to better tolerance of this daily therapy. Yet, in order for TTFields to gain popularity, it is not enough for patients alone to become more accepting; physicians will also need to be open to novel treatments. It is somewhat incongruous that we are so concerned about a therapy that has few adverse effects when many of our newly approved active cancer

molecules are associated with reduced patient safety even if they improve overall survival or HRQoL.[9] Overall, these new data on HRQoL, coupled with the overall survival results of EF-14, strengthen the inclusion of TTFields as an important treatment for our patients with GBM if they are willing to wear the device.

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Clinical Cancer Advances 2018: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology

John Heymach, Lada Krilov, Anthony Alberg,† Nancy Baxter,† Susan Marina Chang,† Ryan Corcoran,† William Dale,† Angela DeMichele,† Catherine S. Magid Diefenbach,† Andrew S. Epstein,† Maura L. Gillison,† David L. Graham,† Joshua Jones,† Andrew H. Ko,† Ana Maria Lopez,† Robert G. Maki,† Carlos Rodriguez-Galindo,† Richard L. Schilsky,‡ Mario Sznol,† Shannon Neville Westin,† and Harold Burstein**

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A MESSAGE FROM ASCO'S PRESIDENT

I remember when ASCO first conceived of publishing an annual report on the most transformative research occurring in cancer care. Thirteen reports later, the progress we have chronicled is remarkable, and this year is no different. The research featured in ASCO's *Clinical Cancer Advances 2018* report underscores the impressive gains in our understanding of cancer and in our ability to tailor treatments to tumors' genetic makeup.

The ASCO 2018 Advance of the Year, adoptive cell immunotherapy, allows clinicians to genetically reprogram patients' own immune cells to find and attack cancer cells throughout the body. Chimeric antigen receptor (CAR) T-cell therapy—a type of adoptive cell immunotherapy—has led to remarkable results in young patients with acute lymphoblastic leukemia (ALL) and in adults with lymphoma and multiple myeloma. Researchers are also exploring this approach in other types of cancer.

This advance would not be possible without robust federal investment in cancer research. The first clinical trial of CAR T-cell therapy in children with ALL was funded, in part, by grants from the National Cancer Institute (NCI), and researchers at the NCI Center for Cancer Research were the first to report on possible CAR T-cell therapy for multiple myeloma. These discoveries follow decades of prior research on immunology and cancer biology, much of which was supported by federal dollars.

In fact, many advances that are highlighted in the *2018 Clinical Cancer Advances* report were made possible thanks to our nation's support for biomedical research. Funding from the US National Institutes of Health and the NCI helps researchers pursue critical patient care questions and addresses vital, unmet needs that private industry has little incentive to take on. Federally supported cancer research generates the biomedical innovations that fuel the development and availability of new and improved treatments for patients. We need sustained federal research investment to accelerate the discovery of the next generation of cancer treatments.

Another major trend in this year's report is progress in precision medicine approaches to treat cancer. Although precision medicine offers promise to people with cancer and their families, that promise is only as good as our ability to make these treatments available to all patients. My presidential theme, "Delivering Discoveries: Expanding the Reach of Precision Medicine," focuses on tackling this formidable challenge so that new targeted therapies are accessible to anyone who faces a cancer diagnosis. By improving access to high-quality care, harnessing big data on patient outcomes from across the globe, and pursuing innovative clinical trials, I am optimistic that we will speed the delivery of these most promising treatments to more patients.

Sincerely,
Bruce E. Johnson, FASCO
ASCO President, 2017 to 2018

ASSOCIATED CONTENT

Appendix
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EXECUTIVE SUMMARY

Approximately 1.7 million people received a cancer diagnosis in the United States in 2017.[1] Today, more than 15 million Americans, nearly one in 20, is a survivor of cancer, which means that they have had or are living with cancer.[2] The number of survivors is growing steadily; experts estimate that there will be 26 million by 2040, with 73% 65 years of age or older.[3]

At the same time, the rate of cancer death has been decreasing, and people are living longer with cancer than ever before. Approximately 64% of US patients diagnosed with cancer in 2005 have lived 10 years or more beyond diagnosis, up from 35% for those diagnosed in 1975.[4]

These trends reflect our and other nations' investments in cancer research and the relentless efforts to advance discovery and care. The volume and pace of cancer research is growing rapidly. For example, the number of medical journal articles with the word "cancer" in the title quadrupled in the last decade, from approximately 28,000 in 2007 to 120,000 in 2017.

Yet more work lies ahead. Because of the aging and growing population, there will be more new patients with cancer every year, both in the United States and worldwide. For every life saved, there are still many people waiting for the next breakthrough for themselves or their loved ones.

This report highlights the most important clinical advances of 2017 and previews where cancer science is headed. New treatments help patients with melanoma and ovarian, lung, bladder, brain, and prostate cancer live longer, and many other new therapies delay cancer worsening or lower the chance of recurrence.

In the span of just 1 year—from November 2016 through October 2017—the US Food and Drug Administration (FDA) approved 31 new therapies for > 16 types of cancer. Among the new approvals are two firsts: an adoptive cell immunotherapy—the ASCO Advance of the Year—and a tumor agnostic therapy, that is, treatment that works against different types of cancers that share a common genetic abnormality.

First Adoptive Cell Immunotherapy and Gene Therapy for Cancer

In August 2017, the FDA approved the first adoptive cell immunotherapy, also known as chimeric antigen receptor (CAR) T-cell therapy, and the first gene therapy for cancer, tisagenlecleucel. This double first approval stems from decades of research on how to train the patient's own immune cells to fight cancer.

Even more important than the historic significance of this achievement is the medical need this unique new therapy is poised to fill. Tisagenlecleucel may be the first treatment to truly turn the tables on recurrent pediatric acute lymphoblastic leukemia (ALL), one of the most common cancers in children. In a clinical trial, cancer in four of five patients went into remission after treatment, which was custom prepared in the laboratory from the patients' own blood cells.

In October 2017, the FDA approved the second CAR T-cell therapy, axicabtagene ciloleucel, to treat adults with certain types of lymphoma. Other CAR T-cell therapies seem promising in clinical trials of people with multiple myeloma. CAR T-cell therapy represents an exciting innovation that has the potential to transform cancer care. It also raises the ongoing issue of cost and reminds us that, as a community, we need to find solutions that will assure that every patient with cancer has access to the care they need. See *Advance of the Year: Adoptive Cell Immunotherapy* for more about these advances.

Precision Oncology

The other historic first among FDA approvals in 2017 marks a milestone in precision oncology. The immune checkpoint inhibitor pembrolizumab became the first cancer treatment to receive a tumor-agnostic indication. It received accelerated approval to treat any type of solid tumor that has mismatch repair deficiency, a defect that undermines the cell's ability to repair DNA damage. This approval provides patients with a wide range of different cancers an effective way to control the disease.

Another promising treatment, larotrectinib, which homes in on a different, rare genomic abnormality in the tumor known as tropomyosin receptor kinase (*TRK*) gene fusion, also seems to work across tumor types and in both adults and children. Larotrectinib has the potential to become the first tumor-agnostic targeted therapy for cancer.

Meanwhile, fundamental cancer biology research is uncovering new molecular pathways that are being explored as potential therapeutic targets. In 2017 alone, the FDA approved > 13 new targeted medicines for people with leukemia and multiple myeloma, as well as ovarian, breast, and lung cancer.

Targeted Agent and Profiling Utilization Registry Study

In 2017, ASCO's Targeted Agent and Profiling Utilization Registry (TAPUR) Study (ClinicalTrials.gov identifier: NCT02693535) continued expanding. As of November 2, 2017, there were > 495 participants enrolled on a study drug at more than 83 sites in 18 states, each offering 17 different targeted therapy options provided by the seven participating pharmaceutical companies.

In addition, the study protocol was revised to lower the age of eligibility for the trial from 18 years to 12 years to extend the opportunity for participation to adolescent patients with advanced cancer in cases in which there is a defined adolescent dose for the study drugs.

The objective for the TAPUR Study is to evaluate molecularly targeted cancer drugs and collect data on clinical outcomes to learn about additional uses of these drugs outside of the indications already approved by the FDA.

The TAPUR Study is registered with a full list of inclusion and exclusion criteria and other information. Prospective patients, researchers, and practices interested in participating can visit the TAPUR website, TAPUR.org, or e-mail the TAPUR Study team at TAPUR@asco.org.

Patient-Centered Care

As life expectancy after a cancer diagnosis continues to improve, there is growing recognition of the need to address patients' emotional and psychosocial needs from the time of diagnosis through treatment and survivorship. *Clinical Cancer Advances 2018* highlights efforts to preserve patient quality of life by avoiding unnecessary treatment or by lowering therapy dose or duration. Furthermore, new tools that engage patients in their own care, such as Web programs for symptom monitoring, psychological support,

and end-of-life planning, are showing benefits for both patients and health care systems.

Finally, we are entering a new era in care in which biomedical research is no longer solely driven by researchers and physicians, but also by patients who are more and more directly engaged in driving progress forward. By donating tissue samples and clinical information, or by helping to design research studies and formulate practice guidelines, patients are providing valuable perspectives and contributing to better care for other patients now and in the future.

Federal Support for Cancer Research Is Critical

Federally funded cancer research has driven many of the major prevention and treatment advances of the past 50 years, and has led to substantial improvements in patient survival and dramatic improvements in quality of life for people with cancer. The National Cancer Institute (NCI) funds studies in areas that private industry has little incentive to address, such as research on cancer prevention, screening, and rare cancers, as well as groundbreaking foundational research.

The US National Institutes for Health (NIH) is the single largest public funder of biomedical research in the world. Federally funded biomedical research helps keep the United States globally competitive by contributing $65 billion in economic growth, supporting 380,000 jobs, and generating 2.21 dollars in local economic growth for every dollar in NIH funding.[5,6] It is estimated that NIH-funded basic research provides a positive return to public investment of 43%.[7]

Research funded by the NIH also fuels the innovation on which companies depend to bring new treatments to the marketplace, helping make the United States the global leader in developing treatments. Studies show that NIH investments in biomedical research stimulate increased private investment: Every dollar of increase in public clinical research stimulates 2.35 dollars of industry investment at 3 years.[7]

> **Cancer Research Funding**
>
> More than nine in 10 Americans (91%) believe that the US government should dedicate substantial funding to diagnose, prevent, and treat cancer. Nearly three in four Americans (73%) say the government should spend more to develop cancer treatments and cures, even if it means higher taxes or adding to the deficit (ASCO's National Cancer Opinion Survey, 2017).

Funding from the NIH and other federal agencies supported > 25% of the top advances featured in this report. Among the most notable are studies that have found:

- Prolonged survival with new approaches:
  - A new treatment regimen helps women with recurrent ovarian cancer live longer.
  - A Web-based tool for self-reporting symptoms during chemotherapy helps patients with advanced cancer live longer.
- Longer hormone therapy reduces the risk of breast cancer recurrence.
- Reduced adverse effects with less treatment:
  - Shortening the duration of adjuvant chemotherapy for stage III colorectal cancer is safe and reduces adverse effects.
  - In patients with melanoma, less extensive surgery lowers the risk of lymphedema without compromising survival.
  - Lowering the radiation dose for oropharyngeal cancer reduces health complications without compromising survival.
- Effective strategies to help patients with advanced cancer understand and cope with their prognosis.
- For cancer-related fatigue, exercise and psychological support are more effective than medication.
- New insights on the adverse effects of certain prostate cancer and lung cancer treatments will help inform treatment and survivorship discussions.

In the last year, Congress has made critical investments to improve and accelerate cancer research through supplemental funding for the Cancer Moonshot Initiative and the 21st Century Cures Act. In addition, Congress included a boost in funding for NIH and NCI in fiscal year 2017; however, despite these funding increases, NCI's budget, when adjusted for inflation, remains below prerecession levels[8] (Fig 1).

One manifestation of this reduced budget is that it is more difficult for researchers to secure funding. For example, in 2015, only 16% of new research proposals received funding compared with 27% in 2001.[9] This decline in funding means that it is more difficult for the field to recruit and retain young researchers, which threatens future progress against cancer. Flat funding and budget cuts translate into less innovation, fewer studies launched, fewer patients enrolled in clinical trials, fewer researchers entering the field, and fewer discoveries.

Predictable funding increases are critical to sustain progress against cancer. Dependable and robust funding is essential for planning and conducting multiyear trials that advance new treatments.

> **A Call to Action to Congress**
>
> Americans are counting on our leaders to invest in biomedical innovation that will deliver the next generation of cancer cures to patients. ASCO urges Congress to give hope to millions of Americans with cancer by continuing to build on its investment in cancer research and providing predictable funding increases to NIH and NCI.

About Clinical Cancer Advances

ASCO develops this annual report, now in its 13th edition, to outline the progress that has been achieved in clinical cancer research and care each year. As a whole, *Clinical Cancer Advances* highlights current trends in the field and previews future directions of cancer research.

The content of this report was developed under the direction of a 20-person editorial board composed of experts in a wide range

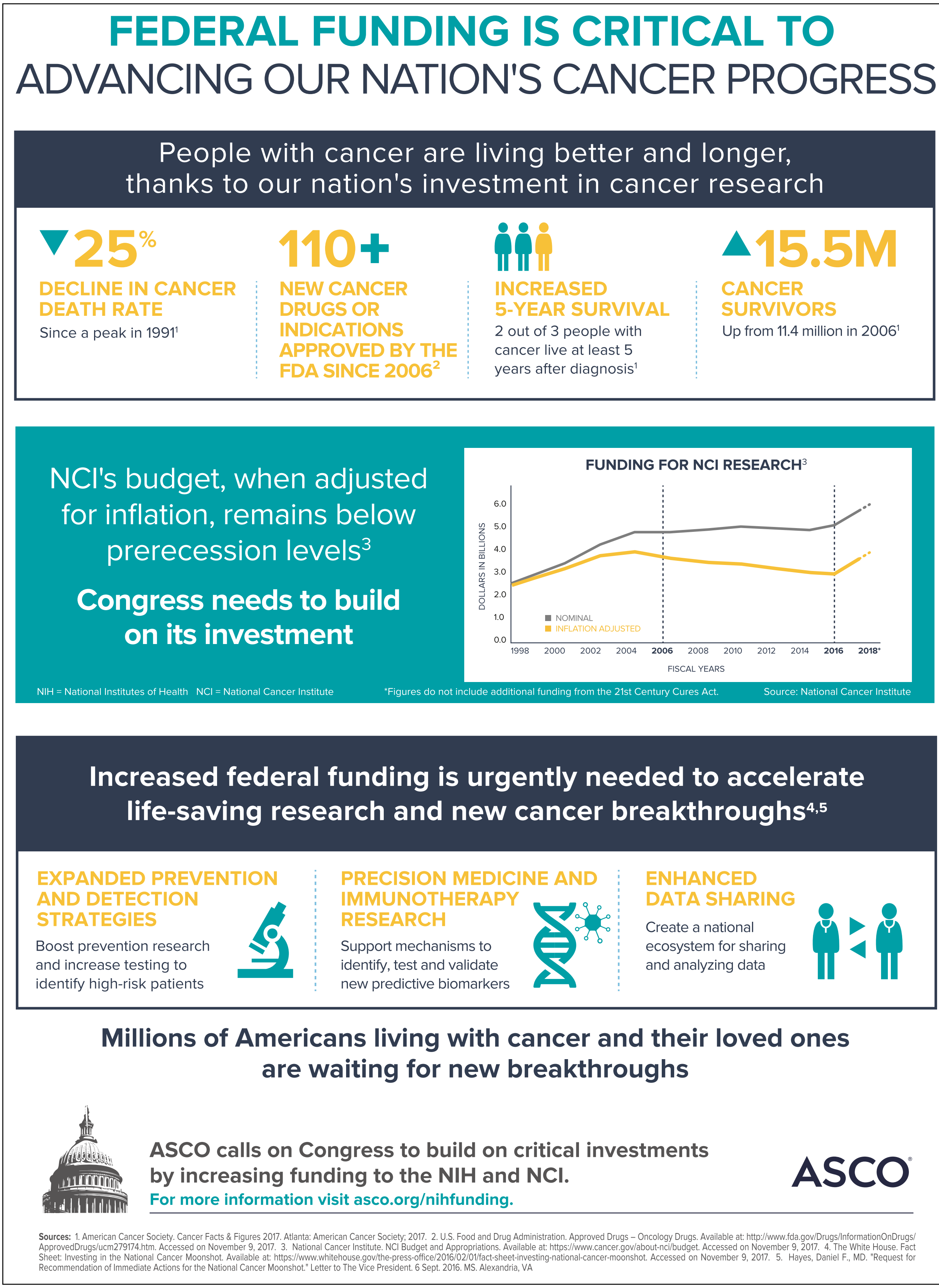

Fig 1. Sustained federal funding is needed to accelerate cancer research. FDA, US Food and Drug Administration.

of cancer types, as well as surgical oncology, radiation oncology, cancer prevention and screening, quality of care, health disparities, tumor biology, and developmental therapeutics. The editors reviewed scientific literature that was published in peer-reviewed journals or presented at major medical conferences from October 2016 through September 2017 and selected advances according to formal criteria. Primarily, advances must improve meaningful patient outcomes, such as survival or quality of life, and have a strong scientific impact.

About ASCO

Founded in 1964, ASCO is committed to making a world of difference in cancer care. As the world's leading organization of its kind, ASCO represents > 40,000 oncology professionals who care for patients living with cancer. Through research, education, and the promotion of the highest-quality patient care, ASCO works to conquer cancer and create a world in which cancer is prevented or cured and every survivor is healthy. ASCO is supported by its affiliate organization, the Conquer Cancer Foundation. Learn more at www.ASCO.org; explore patient education resources at www.Cancer.Net; and follow us on Facebook, Twitter, LinkedIn, and YouTube.

Join Us: Tell Your Representatives to Support Cancer Policy Priorities

More than 100 ASCO members from across the country came to the US capitol in September 2017 for ASCO's annual Advocacy Summit, where members urged Congress to support issues critical to improving cancer research and care. During meetings with members of Congress and staff, ASCO members asked Congress to support policies to increase federal research funding, ensure access to chemotherapy services for patients enrolled in Medicare, and improve the affordability of cancer drugs.

ASCO members have an opportunity to make their voices heard throughout the year by engaging with their members of Congress on key issues related to cancer policy. To learn more about participating in ongoing advocacy efforts, visit asco.org/ACTNetwork.

The Conquer Cancer Foundation

The Conquer Cancer Foundation was created by the world's foremost cancer physicians of ASCO to seek dramatic advances in the prevention, treatment, and cure of all types of cancer. Toward the vision of a world free from the fear of cancer, Conquer Cancer works to conquer this disease by funding breakthrough cancer research and sharing cutting-edge knowledge with patients and physicians worldwide, and by improving the quality of care and access to care, enhancing the lives of all who are touched by cancer.

Over 34 years, > $109 million in funding has been provided through Conquer Cancer's Grants and Awards Program to support clinical and translational scientists, at all levels of their careers and working around the globe, to address the full spectrum of oncology, from prevention through survivorship and end-of-life care. The foundation has given > 1,800 grants and awards in 71 countries. Conquer Cancer grants have helped researchers launch successful careers and make discoveries that benefit patients with cancer.

One of the top patient care advances featured in this report was made possible by funding from Conquer Cancer (see *Patient Engagement Leads to Improved Care*), and several other studies that are highlighted were led by past Conquer Cancer grant recipients who have continued their careers in oncology research.

This report was supported, in part, by funds from Conquer Cancer's Mission Endowment.

ADVANCE OF THE YEAR: ADOPTIVE CELL IMMUNOTHERAPY

This year, ASCO named adoptive cell immunotherapy as the clinical cancer Advance of the Year. After decades of research, this powerful and decidedly unique way of treating cancer has become available to certain patients with an otherwise incurable blood cancer.

What Is Adoptive Cell Immunotherapy?

Immune cells navigate the body looking for anything that does not belong—bacteria, viruses, and even cancer cells. They do so by using their molecular feelers, or receptors, to scan for foreign molecules that intruder cells display on their surface. Once an intruder is detected, a class of immune cells, known as cytotoxic T cells, move in to eliminate it.

Unfortunately, cancers have a number of ways to hide from immune cells and avoid their attack. The recently successful immunotherapy approaches aim to remedy this by taking the brakes off the immune system with the use of targeted drugs, known as immune checkpoint inhibitors.

Whereas adoptive cell immunotherapy also boosts the body's immune defenses against cancer, it does so in a completely different way—by genetically re-engineering a patient's own immune T cells. In the late 1980s, an immunologist was the first to experiment with genetically reprogramming T cells, now known as CAR T cells.

CAR T cells are custom made to work against the cancer in each individual patient. To create these cells, researchers collect immune T cells from the patient and insert an artificial gene into the cells. The gene is designed to endow T cells with chimeric antigen receptors that can detect unique molecules on cancer cells after CAR T cells are multiplied in the laboratory and injected back into the patient. In essence, CAR T-cell therapy is both a gene therapy and an immunotherapy.

When the CAR T-cell receptor attaches to a molecule on a cancer cell, it sends a signal to turn on the destruction machinery of the T cell. Unlike traditional cancer treatments, this living therapy needs to be given to the patient only once, because CAR T cells continue to multiply in the patient's body. As a result, the anticancer effects of CAR T cells can persist and even increase over time.

CAR T-Cell Therapy Is Poised to Transform Childhood ALL Treatment

In 2017, researchers demonstrated that a CAR T-cell therapy known as tisagenlecleucel can eradicate relapsed ALL in children. This represents one of the most remarkable advances in the treatment of childhood cancer in the last decade and could dramatically change treatment paradigms for this disease. Tisagenlecleucel targets a protein, known as CD19, on malignant and normal B cells.

In the United States, ALL will recur in approximately 600 children and young adults per year, despite achieving a response to initial therapy. After a relapse, ALL is difficult to treat, and survival is usually measured in weeks to months. Remission rates with current standard therapies in prior clinical trials have been only 20% with chemotherapy and 33% with targeted therapy.[10,11]

In a clinical trial of children and young adults with relapsed or refractory ALL, cancer went into remission within 3 months of receiving tisagenlecleucel in 52 (82%) of 63 patients, and 75% of patients remained relapse free at 6 months.[12,13] On the basis of these findings, the FDA approved tisagenlecleucel for the treatment of children and young adults with B-cell ALL in August 2017.[14]

This global clinical trial confirmed the high efficacy that was demonstrated in prior, single-institution trials; however, the rate of immune-related adverse effects was high with tisagenlecleucel. Nearly 50% of patients experienced severe cytokine release syndrome (CRS), a complication during which CAR T cells produce a storm of inflammatory molecules. CRS can cause prolonged fever, low blood pressure, difficulty breathing, and problems with multiple organs. If severe, CRS may require intensive medical care, such as the use of a ventilator or medications known as pressors to increase blood pressure, and seizure medication. Although CRS can be serious and even life threatening, doctors now have an effective medicine (tocilizumab) with which to curb and, in most cases, fully reverse the symptoms.

In addition, neurologic complications occurred in 15% of patients in the study. A broad range of neurologic problems, including word recall issues, difficulty speaking, reduction of alertness, delirium, hallucinations, seizures, and coma, have been reported in prior clinical trials with CAR T-cell therapies. In most patients, such symptoms resolved on their own within a few days without long-term consequences, but several deaths have occurred, with severe neurologic complications in other CAR T-cell trials. In this ALL trial, there were no deaths related to either CRS or neurologic complications.

The global ALL trial also helped to prove that patient access to this novel treatment could be broadened. It was the first time CAR T cells were produced from patient blood cells in an industrial manufacturing facility and distributed to patients via a global supply chain that included 25 centers in the United States, Canada, Europe, Australia, and Japan. Until then, the production of CAR T cells was limited to few academic laboratories, without the ability to ship the cell product to patients around the world.

CAR T-Cell Therapy Is Effective Against Hard-to-Treat Lymphoma in Adults

CAR T cells that target CD19 have also been proven to be promising against another hard-to-treat cancer, diffuse large B-cell lymphoma (DLBCL), which is the most common type of non-Hodgkin lymphoma.

In a multicenter clinical trial of patients with DLBCL that worsened after at least two prior therapies, the cancer responded to tisagenlecleucel in 59% of 51 patients and went into remission in 43% of patients.[15] At 6 months, 79% of patients had not had a recurrence of lymphoma. Severe CRS occurred in 25% of patients, and neurologic complications in 13%.

In a different clinical trial, patients with relapsed or refractory DLBCL, refractory primary mediastinal B-cell lymphoma, or transformed follicular lymphoma, received another CAR T-cell product called axicabtagene ciloleucel that also targets CD19.[16] Among the first 92 patients who were treated, the response rate was 82%, with complete remissions occurring in 54% of patients. At a median follow-up of 8.7 months, 39% of patients were still in complete remission. Severe CRS occurred in 13% of patients; neurologic adverse effects occurred in 28% of patients. In late 2017, the FDA approved axicabtagene ciloleucel to treat adults with DLBCL that has not responded to, or has recurred, after at least two prior therapies.[17]

CAR T-Cell Therapy Sends Multiple Myeloma Into Remission

The studies described above all included CAR T cells that were targeted to the B-cell biomarker CD19. A different type of CAR T-cell therapy that targets a biomarker known as B-cell maturation antigen seems to be effective against multiple myeloma. Despite recent advances in treatment, multiple myeloma—a cancer of plasma cells that make antibodies to fight infections—remains an incurable disease, with only approximately one half of patients living 5 years after diagnosis.

In an early clinical trial, the cancer responded to B-cell maturation antigen CAR T cells in 33 (94%) of 35 patients, and went into complete remission in 14 patients[18] (updated data presented at the 2017 ASCO Annual Meeting in Chicago, IL). Only two patients experienced severe CRS, and none experienced neurologic complications from CAR T-cell therapy.

ADVANCES IN CANCER PREVENTION

Cancer prevention efforts, including cancer screening, vaccination, tobacco control, healthy eating, and physical activity, remain key to reducing the effect of cancer and improving outcomes across communities worldwide. In fact, researchers estimate that 50% of cancer cases and deaths in the United States could be prevented if people adopted simple healthy lifestyle choices that include avoiding smoking and alcohol, maintaining a healthy weight, and exercising regularly.[19]

The top three causes of cancer-related death in low-resource countries—liver cancer, stomach cancer, and cervical cancer—are largely preventable through screening or vaccination. In higher-resource countries, two leading causes of cancer-related deaths—lung and colorectal cancer—can be lowered through lifestyle changes, such as increased physical activity and avoidance of alcohol, tobacco, and processed meat. The same healthy habits can help prevent dozens of other cancers. Emerging research suggests that

human papillomavirus (HPV) vaccination, mainly used for the prevention of cervical cancer, may also help reduce head and neck cancers by lowering oral HPV infections.[20] Finally, safe sun exposure practices and avoidance of indoor tanning can substantially lower the risk for melanoma.

Preventive Actions to Lower Cancer Risk

Although most Americans (66%) do not smoke, less than half take other important preventive actions to lower their risk of cancer:

- Use sunblock or limit sun exposure without sunblock (48%)
- Exercise regularly (48%)
- Maintain a healthy body weight (41%)
- Limit alcohol consumption (38%)
(ASCO's National Cancer Opinion Survey, 2017).

Avoidable Cancer Risk Factors: E-Cigarettes May Spur Increases in Smoking

In 2017, two federally funded studies provided the clearest estimates of how e-cigarette use may lead to a future habit of smoking cancer-causing traditional tobacco cigarettes. The first study found that people 14 to 30 years of age who used e-cigarettes were 3.6 times more likely to begin smoking traditional cigarettes than those who never used e-cigarettes (this study was funded, in part, by grants from the NCI, the FDA and the National Institute on Drug Abuse).[21] These findings indicate that e-cigarettes are not merely a substitute for traditional cigarettes, but are also a strong risk factor for future smoking. In fact, experts caution that e-cigarette use may lead to an upsurge in smoking prevalence in the long term.

Another study found that, among US teenagers 12 to 17 years of age, the rate of e-cigarette use is already approaching the rate of tobacco cigarette use; 3.1% smoked e-cigarettes compared with 4.6% who smoked tobacco cigarettes in the last 30 days (this study was funded, in part, by grants from the National Institute on Drug Abuse, NIH, and the FDA).[22] However, among adults, e-cigarette use still lags far behind tobacco cigarette use (6.7% *v* 22.5%). In addition, among those who used more than one tobacco product, 15% of teenagers and 23% of adults used both e-cigarettes and traditional cigarettes.

There is clear evidence that e-cigarettes, smokeless tobacco, and water pipes may cause serious health problems, including cancer. Because of these potential health risks, the FDA began regulating these products, along with other tobacco products, on August 8, 2016. The US Centers for Disease Control and Prevention calls on the public, including parents, health care providers, and teachers, to discourage e-cigarette use among youth. ASCO's Cancer.Net provides information on the risks of e-cigarettes and smokeless tobacco.

Cancer Spending

Almost one half (49%) of Americans believe that the government should spend more money on cancer prevention, and 54% think the government should spend more to help Americans afford cancer screenings and care (ASCO's National Cancer Opinion Survey, 2017).

Avoidable Cancer Risk Factors: Indoor Tanning

UV radiation exposure from indoor tanning is a cause of malignant melanoma. Characterizing the risk of melanoma associated with use of UV radiation–emitting devices is critical for developing policies that reduce the use of such devices, but much of the evidence on this topic has come from case-control studies. In the past year, a large, prospective study was reported that adds new weight to such policy efforts, finding that the risk for melanoma rose with an increasing number of indoor tanning sessions.[23] Compared with those who never used indoor tanning, women who started indoor tanning before 30 years of age had a 30% higher risk for melanoma, which suggests that the harmful effects of indoor tanning are greater at a younger age. For more information on risk factors for melanoma, visit Cancer.Net.

ASCO Issues Statement on Alcohol as It Relates to Cancer Prevention

In 2017, ASCO issued a statement on alcohol and cancer aimed at drawing attention to alcohol consumption as a contributing factor to the overall cancer burden.[24] ASCO cites between 5% and 6% of new cancer cases and deaths globally as being directly attributable to alcohol. This is particularly concerning as 70% of Americans do not recognize drinking alcohol as a risk factor for cancer, according to the National Cancer Opinion Survey, conducted by ASCO in 2017.

Because drinking alcoholic beverages is a potentially modifiable risk factor for cancer, it can be targeted with preventive interventions at both the policy and individual levels to reduce the incidence of cancer. The evidence-based policy recommendations to reduce excessive alcohol consumption listed in the statement, which was published in *Journal of Clinical Oncology*, are:

- Provide alcohol screening and brief interventions in clinical settings;
- Lower the number of alcohol retailers per capita;
- Increase alcohol taxes and prices;
- Maintain limits on days and hours of sale;
- Enhance enforcement of laws that prohibit sales to minors;
- Restrict youth exposure to advertising of alcoholic beverages;
- Resist additional privatization of retail alcohol sales in communities with current government control;
- Include alcohol control strategies in comprehensive cancer control plans; and
- Support efforts to eliminate the use of "pinkwashing" to market alcoholic beverages (ie, discourage alcoholic beverage companies from exploiting the color pink or pink ribbons to show a commitment to finding a cure for breast cancer) given

the evidence that alcohol consumption is linked to an increased risk of breast cancer.

In addition, not only does excessive alcohol consumption cause cancer, it also can delay or negatively affect cancer treatment. Oncologists are uniquely positioned to identify strategies to help their patients reduce alcohol use; address racial, ethnic, gender, and sexual orientation disparities that may place these populations at increased risk of cancer; and serve as community advisors and leaders to raise awareness of alcohol as a cancer risk behavior.

The link between alcohol use and cancer treatment is one of the most-needed areas for future research in the oncology community, particularly in studying the effect of alcohol consumption while undergoing cancer treatment, including chemotherapy, radiation, and surgery. Other underexplored research areas include the effect of alcohol consumption on postoperative morbidity and targeted therapies, such as immunotherapy and radiation. By increasing the community's knowledge of the ways in which alcohol affects cancer and cancer treatments, oncologists and researchers may have a better understanding of its role in disease progression and therapeutic responsiveness and toxicity.

ADVANCES IN CANCER TREATMENT

This year, > 14 million people worldwide will learn they have cancer. According to the latest global statistics, nearly 9 million people a year lose their lives to cancer. That equates to approximately 22,000 cancer deaths per day.[25] The global cancer burden is expected to grow in the future, reaching 21 million patients with cancer and 13 million deaths per year by 2030, as the world's population expands and ages. These sobering statistics underscore the urgency of finding better treatments for patients today and in the future.

The number of new FDA approvals in oncology in recent months is reflective of the scientific fervor and innovation underway to fill this need. From November 2016 through October 2017, the FDA approved a record 18 new cancer therapies and 13 new uses of cancer therapies (Table 1). By comparison, in the same timeframe in the previous year, there were eight new cancer therapies and 13 new uses approved, and a similar number in 2015. Most, if not all, of these new and expanded uses are associated with an improvement in patient survival and/or quality of life.

Also historic, 2017 marked the first approval of a tumor-agnostic therapy and the first adoptive T-cell and gene therapy for cancer, demonstrating that the breakthrough therapy designation and other new approaches in oncology drug development have allowed for a more efficient review and approval process. Research results on other immunotherapies and targeted therapies released in 2017 have changed the treatment paradigms for lung, prostate, and bladder cancer.

Emergence of Tissue-Agnostic Therapies: Treating Patients on the Basis of the Tumor's Genetics, Rather Than Its Location

Historically, cancer therapies have been approved for use on the basis of the tumor's location in the body and stage of cancer. Last year marked a milestone in the history of precision cancer medicine and cancer drug approvals: In May, the FDA approved the first tissue-agnostic treatment, which means that it was approved for use solely on the basis of the genetic make-up of a person's cancer, rather than the type of cancer or its location in the body.[26] Pembrolizumab was approved for the treatment of adults or children with advanced solid tumors that harbor specific genomic changes—mismatch repair (MMR) deficiency or high microsatellite instability (MSI-H).

FDA approval was based on findings from 149 patients with MMR-deficient or MSI-H solid tumors—90 had colorectal cancer and 59 had one of 14 other types of cancer—who were enrolled in five clinical trials. Tumors shrank in 40% of patients, and in 78% of those patients, tumor response lasted ≥ 6 months. In one of the studies that included patients with 12 different types of cancer, 21% of patients experienced a complete remission of cancer (this study was funded, in part, by grants from the NIH).[27]

Cells with MMR deficiency have a lower ability to repair damage to their genetic material or DNA and, as a result, accumulate a high number of mutations and make many abnormal proteins. Recent research has shown that programmed death-1/programmed death ligand-1 immune checkpoint inhibitors, which work by unleashing the immune response to cancer, are particularly effective against tumors with MMR deficiency. The reason for this is thought to be a stronger immune response to tumors with more abnormal proteins that the immune system recognizes as foreign.

With this approval, subsets of patients with various types of cancer that are otherwise resistant to treatment gained a highly effective treatment option for controlling the disease, potentially long term. Testing for MMR deficiency or MSI-H will become part of routine diagnostic workup for many patients with solid tumors.

In 2017, researchers presented the early findings from a study of another treatment that seems to work well across many different types of adult and pediatric cancers. The treatment, called larotrectinib, selectively targets a rare genomic abnormality, the tropomyosin receptor kinase (*TRK*) gene fusion.

It is estimated that this abnormality occurs in approximately 0.5% to 1% of many common cancers. In addition, > 90% of certain rare cancers, such as salivary gland cancer, pediatric breast cancer, and infantile fibrosarcoma, have *TRK* fusions.

Of the first 50 adults and children with 17 different cancer types who received larotrectinib in clinical trials, treatment response rate was nearly 80%.[28] Responses to larotrectinib have been long lasting, with 79% ongoing at 12 months after starting treatment. The most common adverse effects were fatigue and mild dizziness, which were expected, as the normal TRK protein has a role in controlling balance. No patients needed to stop treatment as a result of adverse effects.

In another clinical trial that enrolled 12 young children with different cancers that harbored *TRK* fusions (infantile fibrosarcoma, other sarcomas, and papillary thyroid cancer) the response rate to larotrectinib was 92%, and responses were also durable. At 6 months, the cancer had worsened in only one patient.[29]

These trials that show strong tumor responses in tumors with *TRK* fusions, regardless of histology, represent a major development in the field. These findings pave the way for a new class of

Table 1. FDA Approvals of Cancer Therapies From November 1, 2016, to October 31, 2017

Drug	Indication	Approval Date
New approval		
Rucaparib (Rubraca; Clovis Oncology, Boulder, CO)	For treatment of patients with deleterious BRCA mutation (germline and/or somatic)–associated advanced ovarian cancer who have been treated with two or more chemotherapies.	December 2016
Avelumab (Bavencio; EMD Serono, Darmstadt, Germany)	For the treatment of patients ≥ 12 years of age with metastatic Merkel cell carcinoma. Avelumab is a PD-L1–blocking human immunoglobulin G1λ monoclonal antibody. This is the first FDA-approved product to treat this type of cancer.	March 2017
Niraparib (Zejula; Tesaro, Waltham, MA)	Maintenance treatment for adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.	March 2017
Ribociclib (Kisqali; Novartis, Basel, Switzerland)	In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer.	March 2017
Brigatinib (Alunbrig; Takeda, Osaka, Japan)	For treatment of patients with metastatic anaplastic lymphoma kinase–positive NSCLC who experienced disease progression on or who are intolerant to crizotinib.	April 2017
Midostaurin (Rydapt; Novartis)	For treatment of adult patients with newly diagnosed AML who are FLT3 mutation–positive, as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.	April 2017
Durvalumab (Imfinzi; AstraZeneca, London, United Kingdom)	For treatment of patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or who experience disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.	May 2017
Rituximab and hyaluronidase human (Rituxan Hycela; Genentech, South San Francisco, CA)	For adult patients with follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia.	June 2017
Neratinib (Nerlynx; Puma Biotechnology, Los Angeles, CA)	For extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy.	July 2017
Daunorubicin and cytarabine (Vyxeos; Jazz Pharmaceuticals, Palo Alto, CA)	For treatment of adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes, two types of AML that have a poor prognosis.	August 2017
Enasidenib (Idhifa; Celgene, San Francisco, CA)	For treatment of adult patients with relapsed or refractory AML with an isocitrate dehydrogenase-2 mutation as detected by an FDA-approved test.	August 2017
Inotuzumab ozogamicin (Besponsa; Wyeth, Madison, NJ)	For treatment of adults with relapsed or refractory B-cell precursor ALL.	August 2017
Tisagenlecleucel (Kymriah; Novartis)	For treatment of patients ≤ 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.	August 2017
Abemaciclib (Verzenio; Eli Lilly, Indianapolis, IN)	In combination with fulvestrant for women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression after endocrine therapy.	September 2017
Bevacizumab-awwb (Mvasi; Amgen, South San Francisco, CA)	Approved as a biosimilar to bevacizumab (Avastin), bevacizumab-awwb is the first biosimilar approved in the United States for the treatment of cancer.	September 2017
Copanlisib (Aliqopa; Bayer HealthCare, Berlin, Germany)	For treatment of adult patients with relapsed follicular lymphoma who have received at least two prior systemic therapies.	September 2017
Gemtuzumab ozogamicin (Mylotarg; Pfizer, New York, NY)	Newly diagnosed CD33-positive AML in adults and for treatment of relapsed or refractory CD33-positive AML in adults and pediatric patients ≥ 2 years of age. May be used in combination with daunorubicin and cytarabine for adults with newly diagnosed AML or as a stand-alone treatment of certain adult and pediatric patients.	September 2017
Axicabtagene ciloleucel (Yescarta; Kite Pharma, Los Angeles, CA)	For treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy.	October 2017
New use		
Daratumumab (Darzalex; Janssen, Beerse, Belgium)	In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.	November 2016
Nivolumab (Opdivo; Bristol-Meyers Squibb, New York, NY)	Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.	November 2016
Lenalidomide (Revlimid; Celgene)	Maintenance therapy for patients with multiple myeloma after autologous stem-cell transplantation.	February 2017
Nivolumab (Opdivo)	For treatment of patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or experience disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy.	February 2017
Osimertinib (Tagrisso; AstraZeneca)	For treatment of patients with metastatic EGFR T790M mutation–positive NSCLC, as detected by an FDA-approved test, who experienced disease progression on or after EGFR tyrosine kinase inhibitor therapy.	March 2017

(continued on following page)

Table 1. FDA Approvals of Cancer Therapies From November 1, 2016, to October 31, 2017 (continued)

Drug	Indication	Approval Date
Palbociclib (Ibrance; Pfizer)	HR-positive, HER2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women.	March 2017
Pembrolizumab (Keytruda; Merck & Co, Kenilworth, NJ)	For treatment of adult and pediatric patients with refractory classic Hodgkin lymphoma or those who have experienced relapse after three or more prior lines of therapy.	March 2017
Regorafenib (Stivarga; Bayer HealthCare Pharmaceuticals)	For treatment of patients with HCC who have been previously treated with sorafenib.	April 2017
Avelumab (Bavencio)	For patients with locally advanced or metastatic urothelial carcinoma who experienced disease progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.	May 2017
Pembrolizumab (Keytruda)	In combination with pemetrexed and carboplatin for treatment of patients with previously untreated metastatic nonsquamous NSCLC.	May 2017
Pembrolizumab (Keytruda)	For patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.	May 2017
Nivolumab (Opdivo)	For treatment of HCC in patients who have been previously treated with sorafenib.	September 2017
Pembrolizumab (Keytruda)	For patients with recurrent locally advanced or metastatic, gastric, or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 as determined by an FDA-approved test.	September 2017

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NSCLC, non–small-cell lung cancer; PD-L1, programmed death-ligand 1.

drugs for rare tumors and define a new era in oncology. Equally important, they set a new milestone in precision medicine for pediatric oncology, for which it is just starting to be applied.

A Policy Focus: FDA's New Plan to Increase Medical Innovation

The FDA has launched a new Medical Innovation Development Plan designed to facilitate the development of innovative drugs by updating FDA's regulatory tools and policies. FDA intends to use the new plan to streamline the path to market for targeted therapies and other novel drugs to encourage innovation in therapies. In particular, the plan will focus on facilitating the approval of tumor-agnostic therapies—medicines that work comparatively well in many different types of cancer. As part of the plan, FDA will develop guidance on strategies to improve the efficiency of clinical trials, including adaptive trial designs.

New Treatments Slow Advanced Lung Cancer Growth

Lung cancer is among the most common types of cancer and the leading cause of cancer death in men and women worldwide. Last year, an estimated 156,000 people died of this disease in the United States.[30]

The good news is that these grim statistics have been steadily improving. After decades of increases, rates of lung cancer deaths began to decline in the early 1990s and have been falling, on average, 2.5% each year between 2005 and 2014. The 5-year survival rate increased from only 11% in 1975 to 18% in the most recent time period measured (2007 to 2013).[30] For more information about lung cancer, visit Cancer.Net.

This progress is directly tied to changes in therapy that have occurred during the past two decades, with the development of new therapies that not only work better, but that often also have fewer adverse effects than standard chemotherapy, radiation, and surgery.

In 2017, two new regimens were introduced for the initial treatment of the most advanced form of non–small-cell lung cancer (NSCLC)—a targeted medicine, alectinib, and an immune checkpoint inhibitor, pembrolizumab, combined with chemotherapy. For patients with earlier-stage disease, a clinical trial demonstrated that administering a new immune checkpoint inhibitor, durvalumab, after standard chemotherapy and radiation dramatically slowed cancer growth.

New targeted medicine works better than chemotherapy and with fewer adverse effects. Up to 7% of NSCLCs have a genetic change known as anaplastic lymphoma kinase (*ALK*) rearrangement that results in an abnormal ALK protein that causes cells to grow and spread. The first medicine that targets ALK, crizotinib, was approved by the FDA in 2011, and more potent medicines have been introduced since that time. In 2017, two clinical trials showed that one new ALK medicine, alectinib, is more effective than crizotinib for patients with previously untreated NSCLC, and also causes fewer adverse effects.[32,33] In the larger of the two trials, during a median follow-up of 18 months, 41% of patients who received alectinib had their cancer worsen, or died, compared with 68% of those who received crizotinib.[33] Alectinib was also better at curbing the growth of cancer that had spread to the brain; only 12% of patients had worsening brain metastases compared with 45% of those who received crizotinib.

Changing Paradigms in Lung Cancer Treatment

The first paradigm shift occurred in the mid-1990s with research that demonstrated that giving chemotherapy after surgery, known as adjuvant therapy, helps patients live longer, and that combining chemotherapy with radiation therapy can additionally improve the outlook for some patients with lung cancer. Several new chemotherapies were introduced, such as paclitaxel, docetaxel, gemcitabine, and pemetrexed.

The second paradigm shift in the treatment of advanced lung cancer occurred in 2004, when scientists discovered the association between certain mutations in the epidermal growth factor receptor (EGFR) and response to EGFR-targeted drugs, such as gefitinib. EGFR is a protein that helps cancer cells grow and is mutated in 25% of lung cancers. In the ensuing years, several EGFR-targeted drugs were developed (erlotinib, afatinib, and osimertinib) as well as treatments that target less common genetic alterations (*BRAF* gene mutations [dabrafenib plus trametinib] and *ALK* gene rearrangements [crizotinib, ceritinib, and alectinib]).

Finally, the introduction of immunotherapy in 2015 marks the third paradigm shift in the treatment of lung cancer. Immune checkpoint inhibitors, pembrolizumab and nivolumab, were first approved for the treatment of advanced NSCLC that worsens during or after standard chemotherapy, and atezolizumab was approved in 2016. That same year, the FDA approved the first use of immunotherapy for previously untreated advanced NSCLC, pembrolizumab. Currently, immunotherapy is also being studied in earlier stages of disease. In a clinical trial of patients with locally advanced, stage III NSCLC, the checkpoint inhibitor durvalumab delayed disease worsening by nearly 1 year. The ongoing ALCHEMIST immunotherapy trial (ClinicalTrials.gov identifier: NCT02595944) explores whether giving nivolumab after standard treatment of early-stage lung cancer can reduce recurrences and help patients live longer.

Reflecting on these developments, ASCO's clinical practice guideline for advanced NSCLC was revised in 2017 to add immunotherapy as a standard treatment approach for either first-line or second-line settings.[31]

Role of immunotherapy continues to expand, slowing advanced cancer growth. In 2017, the FDA granted accelerated approval to pembrolizumab combined with standard chemotherapy (carboplatin and pemetrexed) as an initial treatment of metastatic NSCLC.[34] The approval was based on an early clinical trial that found that the chance of cancer worsening was cut nearly in half by adding pembrolizumab to chemotherapy. The median time until cancer worsening was 13 months with pembrolizumab and chemotherapy versus 9 months with chemotherapy alone; however, the incidence of serious treatment-related adverse effects was higher with combined modality treatment (41%) than chemotherapy alone (28%). An international phase III clinical trial is underway to confirm these findings (ClinicalTrials.gov identifier: NCT02578680).

A newer immune checkpoint inhibitor, durvalumab, also seems to have a role in lung cancer treatment. These findings mark the first advance in years for the treatment of stage III, locally advanced NSCLC. This type of cancer accounts for approximately one third of all NSCLCs. The standard treatment of patients with tumors that cannot be surgically removed is chemotherapy with radiation, or chemoradiotherapy. Despite this treatment, cancer quickly worsens, and only 15% of patients are alive 5 years after diagnosis.

In this trial, patients whose cancer did not worsen after chemoradiotherapy were randomly assigned to receive durvalumab or placebo.[35] The median time until cancer worsening was 16.8 months with durvalumab and 5.6 months with placebo, and the median time until patients died or the cancer spread to distant parts of the body was 23.2 months versus 14.6 months, respectively.

Continued Research on Immune Checkpoint Inhibitors

Uses for immune checkpoint inhibitors—treatments that help unleash the body's immune response to cancer—continue to expand to more cancer types, which has affirmed the role of this strategy, and particularly agents that target the programmed death-1/programmed death ligand-1 checkpoint in cancer treatment. Key recent studies in this area are listed in Table 2.

Immunotherapy Changes the Treatment Paradigm for Bladder Cancer

Bladder cancer is another type of cancer for which immunotherapy has transformed the outlook for patients. The most common type of bladder cancer, urothelial cancer, is difficult to treat at advanced stages. With standard chemotherapy, only 5% of patients are alive 5 years after diagnosis. For more information about bladder cancer, visit Cancer.Net.

After 30 years of limited progress, the outlook for these patients is now improving with the arrival of a series of immunotherapies (Table 3). For some patients, immunotherapy has opened a treatment option where none previously existed. For others, it offers a chance to live longer with fewer treatment-related adverse effects.

In May 2016, atezolizumab became the first immune checkpoint inhibitor to receive FDA approval for the treatment of advanced bladder cancer.[49] In 2017, the FDA approved four other immune checkpoint inhibitors for patients with previously treated urothelial cancer that worsened, despite platinum-based chemotherapy—nivolumab, avelumab, pembrolizumab, and durvalumab.[50-53] In a large clinical trial that led to the approval of pembrolizumab, patients who received the immunotherapy lived approximately 3 months longer than those who received chemotherapy. Meanwhile, the rate of serious treatment-related adverse effects was more than three times lower in the pembrolizumab group than in the chemotherapy group (15% *v* 49%).[54]

Recent clinical trials also point to the potential use of immunotherapy as an initial treatment for advanced bladder cancer. As a result of physical frailty and certain health conditions, up to two thirds of patients are not eligible for cisplatin-based chemotherapy,

Table 2. Notable Recent Advances With Immune Checkpoint Inhibitors

Cancer Type	Key Finding	First Author
Breast cancer	Addition of pembrolizumab to standard neoadjuvant therapy for high-risk, HER2-negative breast cancer increased rates of pathologic complete response, especially in women with triple-negative breast cancer—a 50% higher rate.	Nanda[36]
Head and neck cancer	Patients with recurrent or metastatic squamous cell head and neck cancer who received nivolumab lived a median of 2-3 months longer than did those who received standard therapy of investigator's choice.	Gillison[37]
Head and neck cancer	Compared with patients with recurrent or metastatic squamous cell head and neck cancer who received standard therapy of investigator's choice, those who received nivolumab had fewer symptoms and better quality of life for 15 weeks.	Harrington[38]
Kidney cancer	Response rate was higher in patients with advanced kidney cancer who received nivolumab as initial treatment than in those who received standard sunitinib (42% *v* 26%, respectively), and time until cancer worsening was longer (median, 11.6 months *v* 8.4 months, respectively).	Escudier[39]
Liver cancer	In an early clinical trial of patients with advanced liver cancer, response rate to nivolumab was 20%, and adverse effects were manageable.	El-Khoueiry[40]
Lung cancer	In a clinical trial of patients with advanced small-cell lung cancer, 1-year survival rate was 30% for those who received nivolumab and 42% for those who received nivolumab with ipililumab.	Hellmann[41]
Lung cancer	Treatment with checkpoint inhibitor durvalumab after standard chemotherapy and radiation delayed worsening of stage III NSCLC by 11 months.	Antonia[42]
Skin cancer	Compared with patients with advanced melanoma who received adjuvant ipililumab, those who received nivolumab had a higher rate of recurrence-free survival at 12 months (70% *v* 61%, respectively) and a lower rate of severe adverse effects (14% *v* 46%, respectively).	Weber[43]
Skin cancer	In patients with advanced melanoma, 3-year survival rate was higher with nivolumab and ipililumab combined (55%) than with either nivolulmab alone (52%) or ipililumab alone (32%).	Wolchok[44]
Skin cancer	In a clinical trial of patients with advanced Merkel cell carcinoma, response rate to PD-L1 inhibitor avelumab was 32% during a median follow-up of 10 months.	Kaufman[45]
Skin cancer	An early clinical trial suggests that a new PD-1 inhibitor, REGN2810, may be effective against a common skin cancer, cutaneous squamous cell carcinoma. Response rate in patients with advanced disease was 52%.	Papadopoulos[46]
Stomach cancer	A large clinical trial shows that nivolumab is effective as a salvage therapy for people with advanced gastric or gastroesophageal junction cancer that worsens despite chemotherapy. At 12 months, 27% of patients were alive compared with 11% of those who received placebo.	Kang[47]
Stomach cancer	Pembrolizumab showed promising efficacy in a clinical trial of patients with previously treated, advanced stomach or gastroesophageal junction cancer. Response rate was 11%, and 12-month survival rate was 23%.	Fuchs[48]

Abbreviations: HER2, human epidermal growth factor receptor 2; NSCLC, non–small-cell lung cancer; PD-L1, programmed death-ligand 1.

which is the standard initial treatment of this disease. Alternative chemotherapies exist, but are less effective; therefore, many such patients receive only supportive care.

In 2017, the FDA granted accelerated approval to pembrolizumab for this indication.[53] The approval was based on a clinical trial of patients with locally advanced or metastatic urothelial cancer who were not eligible for cisplatin-containing chemotherapy.[55] At a median follow-up of 8 months, treatment response rate was 28%, and responses lasted up to 18 months (median duration not reached). Pembrolizumab was well tolerated, with serious adverse effects occurring in 18% of those treated.

In another clinical trial, atezolizumab also was proven to be effective as an initial therapy for patients with advanced urothelial cancer who cannot receive cisplatin-containing chemotherapy.[56]

Table 3. Recent US Food and Drug Administration Approvals of Immunotherapies for Bladder Cancer

Drug Name (trade name)	Indication	Date Approved
Atezolizumab (Tecentriq; Genentech Oncology, South San Francisco, CA)	For treatment of patients with locally advanced or metastatic urothelial carcinoma who experience progression during or after platinum-containing chemotherapy or within 12 months of treatment with platinum-containing chemotherapy.	May 2016
Nivolumab (Opdivo; Bristol-Myers Squibb, Sunnyvale, CA)	For treatment of patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or who experience disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy.	February 2017
Avelumab (Bavencio; EMD Serono, Darmstadt, Germany)	For patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.	May 2017
Durvalumab (Imfinzi; AstraZeneca, London, United Kingdom)	For treatment of patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or who experience disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.	May 2017
Pembrolizumab (Keytruda; Merck & Co, Kenilworth, NJ)	For patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.	May 2017

At a median follow-up of 18 months, the treatment response rate was 23% and median survival was nearly 16 months. These advances have defined new standards of care for patients with advanced bladder cancer.

A Policy Focus: Promoting Patient Participation in Clinical Trials

Clinical trials are critical for the advancement of new cancer treatments, but only a small percentage of patients (< 3%) in the United States participate in clinical trials.[57] In clinical trials, eligibility criteria define the trial population and protect the safety of trial participants, particularly those who may be more vulnerable to the adverse effects of treatment in a clinical trial; however, overly restrictive eligibility criteria can make trial findings more difficult to apply to the treatment of real-world patients with cancer.

ASCO, in collaboration with the nonprofit advocacy organization, Friends of Cancer Research, issued a joint research statement calling for the use of more inclusive eligibility criteria for cancer clinical trials. The statement, published in *Journal of Clinical Oncology*, provides recommendations to address eligibility criteria in five areas: minimum age requirements for trial enrollment, patients with HIV/AIDS, patients with brain metastases, patients experiencing organ dysfunction, and patients with prior and concurrent malignancies.

ASCO is working with the FDA and clinical trial sponsors to identify additional opportunities to safely expand eligibility criteria for oncology trials.

New Approaches Help People With Brain Cancer Live Longer

Two new regimens extend survival in patients with glioblastoma. Grade IV glioma, or glioblastoma (GBM), is one of the most common and deadliest types of brain cancer in adults. With current therapies, fewer than one in 10 patients live 5 years after a diagnosis of GBM. There are now two new strategies that can possibly lengthen life for people with GBM. For more information about GBM and other brain tumors, visit Cancer.Net.

The first involves a novel technology known as tumor-treating fields (TTFs). These are low-intensity electrical fields that are thought to slow cancer growth by blocking cell division. TTFs are delivered to the brain tumor through the skin from a device that patients wear on their head continuously at least 18 hours a day. Preliminary findings from a clinical trial of TTFs led to the FDA approval of the device in 2015 for use in combination with temozolomide chemotherapy, after surgery, chemotherapy, and radiation, for patients with newly diagnosed GBM.[58]

In 2017, researchers reported longer follow-up findings from the same clinical trial.[59] The risk of death was reduced by 37% for patients who used the device compared with those who received chemotherapy alone, with a median survival of 21 months with TTFs and chemotherapy, versus 16 months with chemotherapy alone. The addition of TTFs also doubled the 5-year survival rate, from 5% to 13%.

The second advance is the discovery that adding temozolomide chemotherapy to short-course radiotherapy results in longer survival than radiotherapy alone in elderly patients with GBM.[60] The prognosis for elderly patients with GBM is poor and questions remain about the optimal treatment of older patients.

In the study, patients who received temozolomide with radiotherapy had a 33% lower risk of death and lived longer than those who received radiotherapy alone (median, 9.3 months *v* 7.6 months, respectively), whereas quality of life was similar between the two groups. Researchers also confirmed prior findings that suggested that a genomic biomarker, methylation of the O6-methylguanine–DNA methyltransferase (*MGMT*) gene, predicts better outcomes in patients with GBM. Among patients with methylated *MGMT*, median survival with radiotherapy plus temozolomide was 13.5 months compared with 7.7 months with radiotherapy alone.

Adding chemotherapy to radiation slows glioma growth. Grade III glioma, or anaplastic glioma, commonly occurs in young adults. This type of brain tumor can grow quickly and can recur as GBM despite treatment.

For patients with anaplastic glioma with a genomic abnormality known as 1p19q codeletion (loss of chromosome arms 1p and 19q) there is clear evidence that adding chemotherapy to radiation therapy improves survival; however, there are conflicting reports of the value of adjuvant (postsurgery) chemotherapy for anaplastic glioma without 1p19q codeletion. Preliminary findings from a large clinical trial have clarified the role of adjuvant temozolomide in this patient population.[61]

The 5-year survival rate was markedly longer when temozolomide was added to radiation therapy (56%) than when patients received radiation therapy alone (44%). Addition of temozolomide after radiation therapy delayed disease worsening by > 2 years (median, 43 months *v* 19 months, respectively). Temozolomide was well tolerated, with serious adverse effects occurring in only 12% of patients. These findings have established this regimen as a new standard of care for patients with anaplastic glioblastoma without 1p19q codeletion.

New Targeted Therapy Regimens for Breast Cancer

For BRCA*-related breast cancer, olaparib is more effective than chemotherapy.* Findings from a large clinical trial of women with advanced, *BRCA*-related breast cancer point to a new type of treatment for the disease—poly (ADP-ribose) polymerase (PARP) inhibitors. Compared with standard chemotherapy, the PARP inhibitor olaparib lowered the risk of cancer worsening by 42% and extended the time until the cancer worsened by approximately 3 months.[62] Severe adverse effects were less common with olaparib, occurring in 37% of patients compared with 50% of those who were treated with chemotherapy. For more information about advanced breast cancer, visit Cancer.Net.

Whereas several PARP inhibitors are already approved by the FDA for the treatment of ovarian cancer, this is the first study to demonstrate clinical benefit from this approach in patients with breast cancer. Several other large clinical trials of olaparib in breast cancer are underway (ClinicalTrials.gov identifiers: NCT02032823 and NCT03167619).

Up to 3% of all breast cancers occur in women who carry inherited changes in genes *BRCA1* and *BRCA2.* These changes undermine the ability of the cell to repair damaged DNA. Because of their underlying defect in DNA repair, cancer cells with *BRCA* mutations are particularly vulnerable to treatments that target PARP, another key component of the cell's DNA repair machinery.

Dual targeted therapy lowers the risk of invasive breast cancer in some women. A clinical trial of nearly 5,000 women with early, human epidermal growth factor receptor 2 (HER2)–positive breast cancer has suggested that adding a second HER2-targeted medicine, pertuzumab, to the standard regimen of the HER2-blocking therapy trastuzumab and chemotherapy may help some women.[63]

Recurrences were reduced by approximately one fifth in patients who received pertuzumab with trastuzumab after surgery compared with those who received trastuzumab and placebo. At 3 years, an estimated 94.1% of patients in the pertuzumab group were free of invasive breast cancer compared with 93.2% of patients in the placebo group. Addition of pertuzumab did not increase the rate of heart problems, which is the greatest concern with HER2-targeted therapy.

Treatment benefit was particularly evident in patients with breast cancer that had spread to lymph nodes—an estimated 92% were free of invasive cancer compared with 90.2% of those who received placebo at 3 years. In contrast, in patients with node-negative cancer, pertuzumab did not improve invasive disease–free survival.

These findings may set a new standard of care for some patients with node-positive, HER2-positive, hormone receptor–negative breast cancer who have a higher risk of developing invasive breast cancer. Meanwhile, researchers are trying to identify biomarkers that may help predict which groups of patients will benefit most from pertuzumab. The good news from this trial is that patients with HER2-positive breast cancer—the group of patients that used to have the worst prognosis—are doing so well on trastuzumab alone.

Research Supports Extended Hormone Therapy for Patients With Higher-Risk Breast Cancer

To lower the chance of cancer recurrence, many women with early-stage breast cancer receive hormone therapy after surgery. Until recently, the recommended standard duration of such therapy had been 5 years, but new research findings suggest that extending hormone therapy may benefit some patients.

In 2016, a large clinical trial found that, in women with hormone receptor–positive, early breast cancer who received the aromatase inhibitor letrozole for 10 years, breast cancer recurrences or new cancers in the opposite breast were reduced by approximately one third compared with women who received 5 years of aromatase inhibitor therapy.[64] Later that year, an even larger trial reported a similar (29%) reduction in the risk of breast cancer recurrence or cancer in the opposite breast for women who received 5 additional years of letrozole after 5 years of aromatase inhibitor therapy (this study was funded, in part, by a grant from the NCI).[65] However, longer hormone therapy did not improve overall or disease-free survival—the primary end point of the study—and was accompanied by a small increase in the risk of blood clots.

In late 2017, researchers reported on an improvement in disease-free survival for women who received extended aromatase inhibitor therapy after tamoxifen.[66] In that clinical trial, 5-year disease-free survival was 83% among women who received anastrozole for 6 years, and 79% among those who received it for 3 years; however, patients in the 6-year therapy group had more adverse effects, including joint and muscle pain.

Taken together, these findings support longer hormone therapy for women with early breast cancer who have a higher risk for recurrence on the basis of tumor features and patient-specific factors. Discussion of therapy duration should take into consideration the adverse effects the patient experienced during initial hormone therapy, as well as ongoing health conditions. If patients are carefully selected for extended hormone therapy, breast cancer mortality can be additionally reduced without overtreatment.

Bevacizumab May Help Some Women With Ovarian Cancer Live Longer

Women with recurrent ovarian cancer have a short life expectancy and limited treatment options. In late 2016, the FDA approved a new regimen that improves their outlook—adding bevacizumab to standard platinum-based chemotherapy. This was the first approval of a new treatment of platinum-sensitive ovarian cancer in more than a decade. Bevacizumab had been previously approved for the treatment of women with platinum-resistant ovarian cancer. For more information about ovarian cancer, visit Cancer.Net.

This new approval was based on a clinical trial in which women received standard chemotherapy alone or bevacizumab with standard paclitaxel plus carboplatin chemotherapy, followed by maintenance therapy with bevacizumab (this study was funded, in part, by a grant from the NCI).[67] Addition of bevacizumab significantly extended median time until cancer worsening to 13.8 months compared with 10.4 months with chemotherapy alone. Overall survival was also longer with bevacizumab than with chemotherapy alone (median, 42 months *v* 37 months), but this difference was not statistically significant; however, the rate of severe adverse effects was higher in the bevacizumab group (96%) than in the standard therapy group (86%), with high blood pressure and fatigue being the most common adverse effects with bevacizumab.

New Maintenance Therapies Keep Recurrent Ovarian Cancer From Worsening

Maintenance therapy for ovarian cancer is critical because of the high rate of recurrence, despite initial response to standard platinum-based chemotherapy. In 2017, the FDA approved a new maintenance treatment, the PARP inhibitor olaparib, for women with recurrent ovarian cancer who responded to platinum-based chemotherapy.[68] Approval was based on a clinical trial in which olaparib was demonstrated to markedly slow cancer growth.[69] Median time until cancer worsening was 19.1 months with olaparib versus 5.1 months with placebo. The most common severe adverse effects of olaparib were anemia and fatigue.

Meanwhile, in a clinical trial of maintenance therapy with the PARP inhibitor rucaparib, the growth of platinum-sensitive, recurrent ovarian cancer was also slowed.[70] Overall, rucaparib delayed cancer worsening by approximately 5 months longer than placebo (10.8 months *v* 5.4 months, respectively). Benefit was greatest among women with *BRCA* mutations (median time until cancer worsening was 16.6 months with rucaparib *v* 5.4 months with placebo), as well as women with tumors that harbored defects in DNA repair machinery (median time until cancer worsening was 13.6 months with rucaparib *v* 5.4 months with placebo). The most common severe adverse effects of rucaparib were anemia and liver enzyme abnormalities. These findings have been submitted to the FDA for the approval of rucaparib in this setting.

A Policy Focus: Learning More About Older Adults With Cancer

More than 60% of cancer diagnoses in the United States occur in people age ≥ 65 years—a population that will grow rapidly over the coming years. Whereas 70% of cancer deaths occur in older adults, and older adults make up the majority of survivors of cancer, the evidence base for treating this population is sparse. Older adults are underrepresented in clinical trials, and trials designed specifically for older adults are rare.

ASCO and the FDA held a workshop in November 2017 to discuss ASCO's recommendations to improve the evidence base for treating older adults. ASCO is continuing to urge federal agencies and the cancer research community to increase the enrollment of older adults in clinical trials and use other strategies to collect evidence on this population of patients.

Precision Medicine Helps People With Melanoma Live Longer

Whereas early-stage melanoma is curable with surgery, patients with stage III melanoma face a much higher chance of recurrence after surgery, and many ultimately die of metastatic disease. New findings suggest that a precision medicine approach that combines two targeted medicines can improve outcomes for a subset of patients.

The study was conducted in patients with tumors that harbored *BRAF* gene mutations, which occur in approximately 40% of all melanomas. *BRAF* mutations turn on a molecular pathway known as mitogen-activated protein kinase. Prior research has demonstrated that blocking this pathway with two medicines in combination—dabrafenib and trametinib—helps patients with metastatic, *BRAF*-mutated melanoma live longer (the FDA approved this regimen in 2014).

In 2017, researchers reported that the combination of dabrafenib and trametinib can also help patients with stage III melanoma by lowering the risk for recurrence after surgery.[71] Estimated 3-year relapse-free survival rates were 58% with targeted therapy and 39% with placebo. Overall survival rates were 86% with targeted therapy versus 77% with placebo.

Combined targeted treatment was associated with a considerable rate of serious adverse effects (36%), including potentially fatal pneumonia. Overall, 26% of patients had to stop treatment earlier than the planned 12-month duration as a result of adverse effects. Currently, there is insufficient evidence to inform the most beneficial duration of adjuvant therapy for stage III melanoma. For more information about melanoma, visit Cancer.Net.

New Treatment Paradigms Help Men With Prostate Cancer Live Longer

Adding hormone therapy to radiation boosts the long-term survival rate. More than 30% of men who receive surgery for localized prostate cancer experience a recurrence of cancer. Patients who experience a local recurrence after surgery receive radiation therapy, but despite the therapy, the cancer eventually worsens in up to 50% of men. For more information about prostate cancer, visit Cancer.Net.

A recent large clinical trial found that adding androgen-deprivation therapy to radiation therapy helps men, who experience a local recurrence after surgery, live longer (this study was funded, in part, by a grant from the NCI).[72] The study enrolled men with prostate-specific antigen levels between 0.2 ng/mL and 4 ng/mL at least 8 weeks after surgery. Men were randomly assigned to receive androgen-deprivation therapy bicalutamide during and 24 months after radiation therapy or radiation therapy and placebo. Survival rate at 12 years was 76% in the bicalutamide group versus 71% in the placebo group. More men in the placebo group developed metastatic prostate cancer (23% *v* 14%, respectively) and more died of the disease (13% *v* 6%, respectively). Late effects of radiotherapy were similar between groups, but gynecomastia (swelling of breast tissue) was much more common with bicalutamide, occurring in 70% of men compared with 11% of those who received placebo.

Whereas other clinical trials are investigating the use of newer hormonal therapies with radiation therapy after prostate cancer surgery (ClinicalTrials.gov identifiers: NCT00541047 and NCT00423475), these findings provide strong evidence to support the combination of androgen-deprivation therapy with radiation therapy for men who experience a local recurrence after surgery.

A new standard of care for advanced prostate cancer. Two large studies presented in 2017 demonstrated that adding abiraterone to standard androgen-deprivation therapy helps men with metastatic prostate cancer live longer. Whereas androgen-deprivation therapy slows prostate cancer growth by preventing the testicles from making testosterone, certain other organs in the body continue making small amounts of testosterone and other androgens. Abiraterone stops the production of both testosterone and other androgens throughout the body by blocking an enzyme that converts other hormones to androgens.

In the first study, patients with high-risk metastatic prostate cancer were randomly assigned to receive androgen-deprivation therapy with either abiraterone or placebo.[73] At a median follow-up of 30 months, men who received abiraterone had a 38% lower risk of death than did those who received placebo. Abiraterone also more than doubled the median time until cancer worsening from 15 months to 33 months.

The second study, which included men with high-risk, locally advanced or metastatic prostate cancer, found that patients who received abiraterone with standard androgen-deprivation therapy had a 37% lower risk of death than those who received androgen-deprivation therapy alone.[74] The 3-year survival rate was 76% with standard therapy alone and 83% with standard therapy plus abiraterone.

Taken together, these findings define a new standard of care for men with metastatic prostate cancer.

Research Informs Decision Making for Early Prostate Cancer Treatment

Men with early (localized) prostate cancer can choose one of three standard treatments, which include surgery, radiation therapy, or active surveillance. A recent clinical trial found no significant differences in 10-year survival with any approach, although active surveillance was associated with a higher risk of cancer worsening and metastasis.[75]

A subsequent analysis of patient-reported outcome data from the same clinical trial showed that adverse effects differed among the three approaches.[76] Surgery had a greater negative impact on sexual function and urinary continence than either radiation therapy or active surveillance. In the active surveillance group, sexual and urinary function declined gradually. Bowel function problems were worse in the radiotherapy group than in the other two groups at 6 months, but subsequently recovered somewhat. There were no significant differences among the treatment groups in anxiety, depression, or general health-related or cancer-related quality of life.

Another clinical trial that compared surgery with active surveillance found that men who received surgery had more sexual dysfunction and urinary incontinence through 10 years than did those who received active surveillance (this study was funded, in part, by grants from the US Department of Veterans Affairs, the Agency for Healthcare Quality and Research, and the NCI).[77] Limitations in activities of daily living through 2 years were also greater in the surgery group.

In addition, two large, population-based studies that observed men with localized prostate cancer for 3 years also found that patterns of adverse effects differed depending on the type of treatment men received.[78,79]

Taken together, these findings from clinical trial participants as well as real-world patients will help clinicians better counsel patients about the risks and benefits of various treatments for localized prostate cancer.

Less Is More: Preserving Quality of Life With Less Treatment

Shorter chemotherapy for colon cancer is safe and lowers the chance of nerve damage. For patients with stage III colon cancer, administering chemotherapy after surgery (adjuvant chemotherapy) lowers the chance that the cancer will come back. The standard 6-month course of adjuvant oxaliplatin-based chemotherapy can cause peripheral neuropathy. Symptoms of this condition, which include pain, tingling, numbness, and muscle weakness, sometimes persist indefinitely. Longer chemotherapy also typically means more diarrhea and fatigue, more doctor appointments, blood draws, and time away from work and social gatherings.

Six clinical trials with 12,800 patients in North America, Europe, and Japan explored whether adjuvant chemotherapy regimens that consisted of either FOLFOX (infusional fluorouracil, leucovorin, and oxaliplatin) or CAPOX (capecitabine and oxaliplatin) could be shortened to 3 months without compromising survival. In 2017, researchers reported on the analysis of pooled data from the trials (this study was funded, in part, by a grant from the NCI).[80]

The chance of being free from colon cancer at 3 years was only slightly lower with 3 months of chemotherapy than with 6 months (74.6% *v* 75.5%, respectively). For patients with a lower risk of cancer recurrence (T1 to T3 N1 colon cancer), the chance of being cancer free at 3 years was nearly identical between the two groups—83.1% in those who received a 3-month course and 83.3% in patients who received a 6-month course.

The rate of clinically meaningful nerve damage differed depending on the type of chemotherapy regimen received, but was consistently lower for people who received 3 months versus 6 months of chemotherapy (15% *v* 45% with FOLFOX and 17% *v* 48% with CAPOX, respectively).

These findings, relevant to approximately 400,000 patients with stage III colon cancer worldwide, should inform conversations between oncologists and their patients. For patients with lower-risk stage III colon cancer, the shorter 3-month course will likely become the new standard of care. For patients with higher-risk cancer, decisions on shorter-duration therapy will have to be carefully weighed against the risks of recurrence, patient ability to tolerate chemotherapy, and patient preferences. For more information about colon cancer, visit Cancer.Net.

Less extensive surgery for melanoma spares patients complications. Many patients with intermediate-thickness melanomas (1.2 mm to 3.5 mm) routinely receive sentinel lymph node biopsy, a procedure that removes the first lymph node to which cancer cells are likely to spread. The lymph node is then checked for cancer. If cancer cells are found in this sentinel node, the patient is more likely to experience a recurrence of melanoma after surgery.

To lower the chances of recurrence in patients with cancer in sentinel nodes, removal of the remaining lymph nodes near the tumor is usually recommended; however, this more extensive surgery increases the risk for complications, particularly long-term swelling of an arm or leg from the build-up of lymph fluid in tissues, known as lymphedema. Experts have therefore questioned the value of this surgical procedure in patients with positive sentinel lymph nodes.

A large clinical trial reported in 2017 suggests that the removal of additional lymph nodes may not be necessary (this study was funded, in part, by a grant from the NCI).[81] At 3 years, the rate of melanoma-specific survival (the percentage of people who had not died of melanoma) was the same (86%) whether patients received additional surgery to remove lymph nodes or were only observed.

Patients who received additional surgery had a lower risk of regional recurrence, but also had more health complications. The rate of lymphedema was four times higher in the surgery group than in the observation group (24% *v* 6%, respectively). Given that lymph node surgery does not improve survival, it

may be possible to avoid this treatment in many patients and spare them an additional surgery with its associated complications.

A Policy Focus: Streamlining Adverse Events Reporting for Cancer Clinical Trials

Regulations require research sponsors to report certain serious adverse events experienced by patients in a clinical trial to the FDA via an expedited process. The current challenge with reporting is the high volume of uninformative reports, which hinders patient safety, imposes a substantial toll on the FDA, research site time, and resources. In March 2017, ASCO held a workshop on streamlining adverse events reporting. Attended by stakeholders from across the cancer research community, including researchers, industry representatives, patient advocates, and officials from the FDA and the NCI, the workshop discussed ways to decrease over-reporting as well as best practices for adverse events reporting for both sponsors and research sites. Recommendations developed through this effort were published in late 2017 in *Journal of Clinical Oncology*.

Fewer women having additional breast surgery after lumpectomy. Performing a second surgery after initial lumpectomy for early breast cancer was previously common. Second surgery was often recommended as a result of positive or close margins, which means that some cancer cells were found along the edge of the cancer tissue removed by lumpectomy; however, there has been controversy over what constitutes a negative margin.

In 2014, the Society of Surgical Oncology and the American Society of Radiation Oncology published an evidence-based consensus statement, endorsed by ASCO, that recommended that if there are no cancer cells adjacent to any inked edge/surface of the surgical specimen, the margins should be considered negative and a second surgery is not required.[82]

A recent large, population-based study assessed the effect of this recommendation on the rates of breast cancer surgery (this study was funded, in part, by a grant from the NCI).[83] From 2013 to 2015, the rate of initial lumpectomy remained stable at 67%, but the rate of second breast surgery declined by 16%, and fewer women underwent a subsequent mastectomy. This study demonstrates the important role of clinical practice guidelines in reducing overtreatment.

Delaying rectal cancer surgery lowers the risk of complication. Radiation therapy before surgery lowers the risk of local recurrence in patients with rectal cancer. In the past, it was considered important to perform surgery soon after the completion of radiation therapy, but a new study in Sweden found that delaying surgery by a few weeks is safe and results in fewer complications.[84]

There was no difference in local recurrence between patients who received the standard short-course radiation therapy with surgery within 1 week and those who received surgery 4 weeks to 8 weeks after either short-course radiation or long-course radiation therapy. Patients who received short-course radiation therapy with delayed surgery had a nearly 40% lower risk of complications after surgery than those who received standard short-course radiation without a delay in surgery.

Although common in Europe, short-course radiation therapy before surgery is not used in the United States, where the standard approach is chemotherapy and radiation. An ongoing clinical trial is exploring whether radiation therapy can be eliminated from the treatment of high-risk, locally advanced rectal cancer (ClinicalTrials.gov identifier: NCT01515787).

Lowering radiation therapy dose for throat cancer reduces long-term complications. HPV-associated oropharyngeal cancer responds well to treatment, but the standard radiation therapy administered with chemotherapy can lead to debilitating long-term complications. As patients with HPV-associated oropharyngeal cancer tend to be younger, they may carry the burden of these complications for decades.

Two separate clinical trials found that lowering the standard radiation dose by 15% to 20% in patients with a favorable prognosis (ie, a complete clinical response is achieved with initial chemotherapy) does not compromise survival. In the first study, the 2-year survival rate was 94% for patients who were treated with 54 Gy and 96% for those who received ≤ 54 Gy, and adverse effects were milder with the lower dose (this study was supported, in part, by grants from the NCI and the US Department of Health and Human Services).[85] At 12 months, markedly fewer patients in the lower-dose group had difficulty swallowing solids (40% *v* 89%, respectively) or impaired nutrition (10% *v* 44%, respectively) compared with patients who received higher doses of treatment. In the second study, where patients with a more favorable prognosis received a dose of 54 Gy and others received 60 Gy, cancer had not worsened for 92% of patients overall at 2 years.[86]

If confirmed in a larger clinical trial, these findings will lead to a change in the standard of care for patients with lower-risk, HPV-related oropharyngeal cancer (eg, those with a minimal smoking history and small tumor size). For more information about oropharyngeal cancer, visit Cancer.Net.

Recent ASCO Clinical Practice Guidelines

Clinical practice guidelines help to distill knowledge about a particular clinical issue and provide recommendations to help clinicians deliver the best treatment and care to every patient. ASCO develops its clinical practice guidelines through a rigorous, systematic review of relevant medical literature and clinical interpretation from a multidisciplinary panel of experts and patient representatives. In 2017, ASCO issued more than 14 clinical practice guidelines, guideline updates, and provisional clinical opinions (Table 4). To view ASCO guidance by clinical area, visit https://www.asco.org/practice-guidelines/quality-guidelines/guidelines.

Table 4. ASCO Clinical Practice Guidelines, Updates, Endorsements, and Provisional Clinical Opinions from January to October 2017

Publication Date	Guideline
Guideline	
January 17	Management of Small Renal Masses: American Society of Clinical Oncology Clinical Practice Guideline Summary
January 30	Screening to Prevent Invasive Cervical Cancer: ASCO Resource-Stratified Clinical Practice Guideline
February 6	Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology
March 6	Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline
March 17	Primary Prevention of Cervical Cancer: American Society of Clinical Oncology Resource-Stratified Guideline
August 10	Treatment of Nonmetastatic Muscle-Invasive Bladder Cancer: American Urological Association/American Society of Clinical Oncology/American Society for Radiation Oncology/Society of Urologic Oncology Clinical Practice Guideline
September 11	Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline
Guideline Update	
March 27	Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update
April 11	Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update
April 24	Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stages I to IIIA Resectable Non–Small-Cell Lung Cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update
July 10	Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update
July 31	Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update
August 14	Systemic Therapy for Stage IV Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update
Guideline Endorsement	
February 27	Head and Neck Cancer Survivorship Care Guideline: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Cancer Society Guideline
Provisional Clinical Opinion	
April 25	Second-Line Hormonal Therapy for Men With Chemotherapy-Naïve, Castration-Resistant Prostate Cancer: American Society of Clinical Oncology Provisional Clinical Opinion

For additional advances in cancer treatment, please see Appendix Table A1 (online only).

ADVANCES IN PATIENT CARE

Communication and Coping Tools Improve End-of-Life Planning

Having accurate information about prognosis is crucial for patients with late-stage cancer. Having conversations about the end of life helps patients set appropriate goals and potentially avoid intensive medical treatments and hospital death.

However, many patients are misinformed about or misunderstand their prognosis, and others have difficulty coping with the realization that their illness is terminal. Recent research has focused on interventions and tools that may help overcome this gap in patient-doctor communication.

In one study, a communication coaching intervention helped patients with late-stage cancer actively seek information and express preferences about their care (this study was funded, in part, by a grant from the NCI).[87] Oncologists in the intervention group received brief, individualized, skill-based communication training that focused on being receptive to patient questions and concerns. Patients received individualized communication coaching that incorporated a list of questions related to cancer care and end-of-life issues. Oncologists and patients in the control group did not receive any communication training or prompting.

During a subsequent office visit, nearly three times as many patients in the intervention group than in the control group (17% *v* 6%, respectively) asked about prognosis, and more than twice as many (70% *v* 33%, respectively) brought up topics that were covered by the communication coaching, such as cancer treatment, current cancer state, and preferences about care at the end of life. Whereas validation of these results in other settings is necessary, they underscore the value of combined patient–doctor interventions to enhance communication.

New online tools are another way of helping patients plan for the end of life. In a recent study of elderly patients with chronic and/or serious conditions, 35% of those who used the interactive, patient-centered advance care planning Web site, PREPARE, along with an easy-to-read advance directive, succeeded in assembling advance planning documentation compared with 25% of those who used the advance directive alone (this study was funded by a grant from the US Department of Veterans Affairs Office of Research and Development).[88] Given that the Web site used in this study is free to the public and requires no physician involvement, it represents a method of improving end-of-life care with minimal health care system resource expenditure.

Research shows that certain coping strategies can help patients with incurable cancer who accurately understand their diagnosis to be terminal (this study was funded, in part, by grants from the NIH, NCI, and the National Institute of Nursing Research).[89] For example, patients who used positive reframing (ie, looking for something good in their situation) and active coping (ie, taking action to try to make their situation better) had improved quality of life and less depression.

It is important that doctors communicate the availability of these tools and help patients both understand and cope with advanced cancer and a terminal prognoses. A new ASCO guideline provides oncologists with recommendations regarding core communication skills that apply across the continuum of cancer care, including discussion of goals of care and prognosis, treatment

selection, and end-of-life care.[90] For more information on coping with cancer, visit Cancer.Net.

CancerLinQ Partners With Federal Agencies and Medical Specialty Societies

In 2017, one of the main focus areas for CancerLinQ was partnering with federal agencies, professional societies, and life sciences companies. The goal of these collaborations was to convene the cancer community around solutions for improving the quality of care for patients with cancer. By leveraging the expertise of the many stakeholders that span the care continuum, all of whom affect key decision points in a patient's care, we can help make CancerLinQ a system that encompasses all of cancer care. The effort was successful, with 10 collaborations formally signed and announced between June 2016 and June 2017 with the following organizations:

- American Academy of Physician Assistants
- American Society of Radiation Oncology
- Cancer Informatics for Cancer Centers
- College of American Pathologists
- US Food and Drug Administration
- Hematology/Oncology Pharmacy Association
- National Comprehensive Cancer Network
- National Cancer Institute
- Oncology Nursing Society
- Society of Gynecologic Oncology

The organizations with which CancerLinQ has partnered are invited to participate in the CancerLinQ Oncology Leadership Council, the official body of strategic advisors that comprise member representatives from CancerLinQ's official partner organizations and advisory groups. This is the first time that a coalition of this nature has been created and convened. As CancerLinQ creates this community of learning in cancer, these foundational partners offer incredible thought leadership and represent the importance of a team-based approach to delivering high-quality care.

Managing Common Adverse Effects and Complications

Radiation therapy for lung cancer increases the risk for heart problems. Radiation has been the backbone of treatment of stage III NSCLC for three decades. Despite the known harmful effects that chest radiation can have on the heart, patients with stage III NSCLC still receive high doses of radiation because it is believed that few live long enough to experience heart complications (life expectancy is < 2 years). A pair of studies published in 2017 challenge this notion by showing that heart problems are relatively common in this patient population and occur earlier than historically understood.

In an analysis of patients who were treated in six clinical trials from 1996 to 2009, 21% of those who received a high dose of radiation (≥ 20 Gy) developed symptomatic heart problems within 2 years (this study was funded by a grant from the NIH).[91] Heart problems were independently linked to high doses of radiation and underlying risk (eg, smoking and cardiovascular disease).

A second analysis of patients who were treated in four clinical trials from 2004 to 2013 demonstrated similar results; 11% developed severe heart problems within 2 years (this study was funded by a grant from the NIH).[92] As in the other study, patients who received a higher radiation dose and/or had pre-existing heart disease were more likely to develop heart problems. Furthermore, both cancer worsening and heart problems were linked to shorter survival.

These findings will inform treatment and survivorship discussions between physicians and patients with stage III NSCLC. When selecting radiation dose, controlling tumor growth should be balanced with minimizing the risk for heart problems, particularly in patients with an underlying risk of heart disease.

A recent guideline from ASCO recommends that, before the start of therapy, doctors should discuss the potential for heart problems with patients who are at increased risk for such complications and establish a tailored and detailed plan to monitor them during and after cancer treatment.[93]

Single radiation treatment relieves symptoms of spinal cord compression. As many as one in 10 people with advanced cancer develops spinal cord compression. This condition is a major detriment to quality of life, causing back pain, numbness, tingling, difficulty or inability to walk, and sometimes bowel or bladder incontinence. Radiation therapy can prevent or relieve these symptoms, but it typically requires multiple trips to the clinic for treatment.

Research presented in 2017 demonstrated that a single radiation treatment may be sufficient for patients with a short life expectancy.[94] In a large clinical trial, one-time radiation treatment was as effective as 5 days of treatment in terms of helping patients stay mobile, and median survival was not different between the two groups (approximately 3 months). Shortening radiation therapy allows patients with cancer-related spinal cord compression to spend less time in the hospital and more time doing things they enjoy.

For cancer-related fatigue, exercise and psychological support work best. Cancer-related fatigue is different from feeling tired after staying up too late. It is a persistent feeling of physical, emotional, or mental exhaustion that interferes with one's daily activities and does not improve with rest. Most people who receive cancer treatment experience fatigue, and approximately one third of survivors of cancer experience fatigue that lasts for years after finishing treatment.

Numerous approaches for treating cancer-related fatigue have been tested, with variable outcomes; therefore, it has not been clear which treatments work best. An analysis of 113 randomized clinical trials compared the four most commonly recommended

treatments, which are exercise, psychological intervention, combined exercise and psychological intervention, and medication (this study was funded in part by grants from the NIH).[95]

Exercise, psychological support, and the combination of the two approaches improved cancer-related fatigue during and after cancer treatment. Benefits of these treatments were greater for patients with nonmetastatic disease and varied by intervention mode and timing; however, medications were much less effective than behavioral interventions.

These findings confirm a large body of literature in the field and suggest that exercise and psychological interventions should be used before pharmaceutical interventions, which provide minimal benefit. These recommendations are relevant to many patients with cancer.

ASCO recommends that health care providers assess the patient's level of fatigue at diagnosis and repeat this assessment yearly and at any time there are symptoms of fatigue throughout treatment and into recovery.[96] For more information about cancer-related fatigue, visit Cancer.Net.

ASCO Launches Center for Research and Analytics

In June 2017, ASCO announced the launch of its new Center for Research and Analytics (CENTRA) to make an array of cancer data available to the oncology community and provide consultation and support for research and analysis. The CENTRA team will help analyze and build an evidence base that can help to support cancer policy development, advance the practice of oncology, and improve cancer care for patients. This supports ASCO's continuing commitment to helping to advance the field of oncology and improve cancer care through the generation and application of high-quality evidence.

Requests can be made through CENTRA for data from ASCO sources, such as our quality programs, annual census of oncology practices, and scientific meeting abstracts and presentations. All research requests will be evaluated before being fulfilled.

For more information or to submit requests, please contact CENTRA@asco.org.

Patient Engagement Leads to Improved Care

Web-based symptom reporting extends survival. The value of patients reporting their own outcomes is increasingly recognized in oncology, and there is interest in integrating patient-reported outcomes into routine practice. A recent study demonstrated that a Web-based, patient-reported outcomes tool can help patients with advanced cancer live longer.[97]

With the standard approach of assessing symptoms only during office visits, the health care team can be unaware of patients' symptoms up to half of the time. In a clinical trial, the Web-based tool enabled patients to report common symptoms in real time and triggered alerts to clinicians if symptoms worsened (this study was supported by ASCO's Conquer Cancer Foundation). When appropriate, clinicians took action to relieve symptoms, such as lowering the chemotherapy dose or providing supportive care.

Patients with metastatic cancer who used the tool while receiving chemotherapy lived a median of 5 months longer than those who did not use the tool (31 months *v* 26 months, respectively). This improvement in survival was greater than that associated with nearly all cancer drugs that received FDA approval in 2016.

Researchers previously reported that the use of the same tool was associated with better quality of life and fewer visits to the emergency room and hospitalizations. The findings confirm that patient-reported outcomes should be the standard of care for patients with late-stage cancer. A nationwide clinical trial that uses an updated tool that works on both personal computers and mobile devices is under way in community practices across the United States.

After cancer diagnosis, an online support program lowers distress. Patients experience major distress when they first learn of their cancer diagnosis. Yet amid all the tests, treatment appointments, and family or work decisions, little attention is paid to one's psychological and emotional well-being. In fact, as a result of patients' time constraints and the lack of availability and resources for psychological support, few patients who are newly diagnosed with cancer receive any psychological support.

To address this need, researchers are looking into leveraging Internet-based technologies to provide support to more patients and improve their quality of life. In a recent study, an 8-week Web-based stress management program that was designed by psychologists and oncologists improved quality of life and lowered distress for patients who were newly diagnosed with cancer.[98]

The program covered different topics, such as bodily reaction to stress, cognitive stress reduction, feelings, and social interactions. For each weekly topic, participants received written and audio information, then completed exercises and questionnaires.

The study demonstrated that delivering psychological support via an Internet-based program is feasible, but more research is needed to refine and scale up such an approach for broad use. Researchers already have plans to translate the program into other languages (it is currently available only in German).

Crowdsourcing advances cancer research. Progress against rare cancers is often slow because of a combination of scarce funding and a limited availability of patients and tumor samples for research. An attractive solution to this problem is crowdsourcing. More and more people with rare and common cancers today have the opportunity to rapidly and directly affect research by sharing their tumor tissue samples and medical and/or genetic information to help others with the same or similar diseases. In return, researchers share what they learn with participants.

The Metastatic Breast Cancer Project collects health records and tumor and saliva samples to learn why some patients respond differently to cancer treatments than others. The project engages patients to participate via social media, newsletters, blogs, and advocacy organizations.

Two other such projects focused on sarcoma are run by researchers with the support of patient advocacy organizations, the Angiosarcoma Project and the Leiomyosarcoma Direct Research.

Another emerging type of crowdsourced research engages members of the general public, so-called citizen scientists, to gather ideas, design studies, and perform research-related tasks, such as

analysis of scientific images or quantitative data. This approach is particularly helpful in pathology research studies that require manual review of a large quantity of images. The Cell Slider project recruited approximately 100,000 people to classify images of breast tumor tissue according to estrogen receptor status. To assess the volunteers' performance, researchers compared their classification with that of trained pathologists and found that citizen scientists were able to classify tumors with high accuracy.[99] For additional notable advances in patient care, please see Appendix Table A1.

LOOKING TO THE FUTURE

New Type of Medicine Tackles Undruggable Molecular Targets

Although targeted therapies have had a profound effect on cancer medicine, only approximately 20% of proteins in cancer cells can be targeted by currently available medicines. Many of the undruggable targets include important molecules in pathways that suppress (eg, TP53 and APC) or promote (eg, RAS and MYC) tumor growth. One of the reasons these targets are undruggable is that, historically, it has been difficult to block these pathways with small molecules, and protein drugs do not easily penetrate the cell.

A new class of drugs, known as stapled peptides, has emerged as a promising way to target protein-protein interactions. These small proteins have an artificial chemical bridge, or staple, that holds them in a specific shape that allows them to penetrate the cell.

In an early clinical trial, researchers demonstrated for the first time that a stapled peptide is effective in patients.[100] The peptide targeted the interaction between MDM2 and MDMX-TP53 in patients with solid tumors and lymphoma without p53 mutations. The treatment, ALRN-6924, stalled cancer growth in 45% of 55 patients. A larger clinical trial is under way (ClinicalTrials.gov identifier: NCT02264613).

Emerging Role for Precision Medicine in Cancer Prevention

The concept of precision medicine as applied to cancer prevention is in its nascent stages. In this first phase, scientists are focusing on inherited cancer syndromes, such as *BRCA*-related breast and ovarian cancers and Lynch syndrome.

For patients with inherited genetic susceptibility to cancer, the hope is to one day replace crude, one-size-fits all cancer risk reduction approaches, such as preventive surgery, with personalized approaches that take into account not only a person's genetic makeup and family history, but also the composition of microbes in their body, their diet, lifestyle, and environmental factors.[101]

Scientists are only beginning to understand how the complex interplay of all these factors raises or lowers the chance of developing cancer in an individual with an inherited cancer gene mutation. It is also not clear why changes in genes with broad functions, such as the DNA repair and MMR genes, predispose people for certain, but not all cancers.

Large-scale genomics studies are providing insights by which to fine-tune cancer risk assessment for each person. For example, it seems that certain changes in mitochondrial DNA lower the risk of breast cancer in patients with *BRCA* mutations. Genomic information, along with reproductive and family history, lifestyle, and other factors, may help patients decide whether and when to have preventive surgery.

Scientists are also exploring the possibility of using immune-based approaches, such as vaccines for cancer prevention in healthy people with cancer predisposition syndromes.[102] The idea is to harness the immune system to recognize and eliminate pre-malignant cells on the basis of their molecular characteristics. With the new national investment in cancer prevention through the Cancer Moonshot initiative and cutting-edge technologies, such as sequencing the genomes of individual cells, the opportunity to advance this field is closer than ever.

Understanding Health Disparities: Path to Better Care For All

Cancer is becoming one of the most pressing health care challenges worldwide. Between 2005 and 2015, the number of patients with cancer increased worldwide by 33%.[103] According to the Global Burden of Disease study, issued in late 2017, cancer is the second leading cause of death from noncommunicable diseases, which cause 72% of deaths worldwide.[25]

Whereas many countries have experienced decreases in cancer mortality over the last decade, cancer deaths increased in Sub-Saharan Africa and certain other regions lacking in health care infrastructure (this study was funded in part by a grant from the NIH).[103] Seven of 10 cancer deaths occur in regions of Africa, Asia, and Central and South America, where access to cancer screening and treatment is limited.[104]

Even within high-resource countries, such as the United States, certain communities experience greater cancer incidence, shorter survival, and more deaths from cancer. During the last 60 years, socioeconomic, education, and racial/ethnic inequities in cancer mortality have persisted and even widened in some cases.[105]

Impact of Cancer Care Cost

Among Americans who have never had cancer, 35% are not confident they would receive timely, best-in-class care if diagnosed with cancer in the future. Of serious concern, 27% of Americans who either had cancer themselves or have/had a family member with cancer have taken specific actions to lower treatment costs:

- 9% have skipped doctor appointments;
- 8% have refused treatment;
- 8% have postponed filling or not filled prescriptions;
- 8% have skipped doses of prescribed medications; and
- 7% have cut pills in half.

(ASCO's National Cancer Opinion Survey, 2017).

Recently published studies reveal that the root causes of cancer disparities in the United States are complex. Researchers found that black patients across all socioeconomic groups have higher cancer mortality than white patients. Another study found that people from the poorest communities were more likely to be diagnosed with advanced cancer, regardless of whether they had health insurance.

ASCO Issues Recommendations for Reducing Cancer Disparities Among Sexual and Gender Minority Populations

Sexual and gender minority (SGM) populations, including individuals who are lesbian, gay, bisexual, transgender, and intersex, bear a disproportionate cancer burden that stems from several factors, such as lower rates of cancer screening and a hesitancy on the part of SGM patients to disclose their sexual orientation to providers because of a fear of stigmatization. On April 3, 2017, ASCO issued recommendations to address the needs of SGM populations as they relate to cancer. The recommendations, published in a policy statement in *Journal of Clinical Oncology*, are designed to focus attention on the challenges that face the SGM community, including discrimination and greater risk of anxiety and depression, resulting in disparate care. The statement also provides concrete steps that can help minimize health disparities among SGM individuals.

A Policy Focus: Giving Medicaid Patients Equal Access to Clinical Trials

Most private insurance plans and Medicare are required to cover the routine costs of care for patients who participate in clinical trials. Routine care includes items and services that a payer would cover for a patient who is not enrolled in a clinical trial, such as office visits, radiology exams, and laboratory tests; however, Medicaid is not required to cover these routine costs for patients.

For researchers to understand how different populations respond to cancer treatment and address disparities in cancer outcomes, all types of patients should have the opportunity to participate in cancer trials. Unfortunately, patients from racial and ethnic minority groups that are over-represented in the Medicaid program make up just a small subset of clinical trial participants.

ASCO strongly encourages policymakers to guarantee that Medicaid covers routine care costs for patients in clinical trials so that more patients with Medicaid can participate in cancer research.

In addition, patterns of disparity have been changing. For example, during the 1950s, black people had lower all-cancer mortality than did white people, but since the 1960s, all-cancer mortality rates have been significantly higher for black people than for white people across all socioeconomic groups. Differences are particularly pronounced for some cancers. Within each socioeconomic group, black women have a two times higher cervical cancer mortality and a 50% higher breast cancer mortality rate than white women, and black men have a two times higher prostate cancer mortality rate than white men.[105]

Socioeconomic disparities have also reversed over time. In 1950, people in the most-deprived socioeconomic group had a 27% lower cancer mortality rate than those in the most affluent group, but by 2010 to 2014, the most deprived group had a 22% higher cancer mortality than their most affluent counterparts.[105]

Although patients from disadvantaged communities benefit most from health insurance coverage, insurance alone does not overcome the mortality gap. In one study, patients in the poorest communities were more likely to have advanced cancer at diagnosis and less likely to receive cancer-directed surgery than those from the least disadvantaged communities, regardless of health insurance status (this study was funded, in part, by a grant from the NIH/NCI).[106] Another analysis demonstrated that among people with no health insurance, black patients had rates of cancer mortality that were similar to those of white patients, but had higher mortality rates among either Medicaid or private insurance groups[107].

Even with access to health care, patients may not seek care for many reasons that include having insurance but no health care available nearby, not knowing how to access the health care system, or lack of trust in the health care system.

Other research suggests that socioeconomic disparities in cancer death rates may, in part, be a result of modifiable behaviors that increase the risk of cancer. The 2015 National Health Index Survey showed that prevalence of smoking, obesity, physical inactivity, and inadequate intake of fruit and vegetables was higher among people with lower education and income levels, and rates of cancer screening were lower.

Taken together, this body of research suggests that addressing cancer disparities and achieving equity calls for multifaceted approaches that are focused on efforts to improve prevention, screening, and access to high-quality cancer care.

A Policy Focus: Addressing Health Disparities in Cancer Care

Significant cancer health disparities continue to exist in certain populations. Race, ethnicity, socioeconomic status, and geography all affect patient health outcomes, and racial and ethnic minorities and individuals of lower socioeconomic status experience worse cancer outcomes.

To address this issue, ASCO, with the American Association for Cancer Research, the American Cancer Society, and the NCI, released a joint statement to foster cooperation across the cancer research community to ensure that all patients, regardless of demographics, socioeconomic status, or the communities in which they live, benefit from cancer research (the statement was published in *Journal of Clinical Oncology*[108]).

The statement called for defining and improving data measures and tools for cancer disparities research, addressing disparities in cancer incidence, addressing cancer survival disparities, improving community engagement in cancer research, and redesigning clinical trials to acknowledge and address cancer disparities.

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Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

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Appendix

Table A1. Additional Notable Advances (October 2016 to October 2017)

Area of Research	Study Title	Reference
Screening	Analysis of plasma Epstein-Barr virus DNA to screen for nasopharyngeal cancer	Chan KCA, et al: N Engl J Med 377:513-522, 2017
Treatment	Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia	Kantarjian H, et al: N Engl J Med 376:836-847, 2017
	Pomalidomide for symptomatic Kaposi's sarcoma in people with and without HIV infection: A phase I/II study	Polizzotto MN, et al: J Clin Oncol 34:4125-4131, 2016
	Phase Ia and Ib studies of the novel carcinoembryonic antigen (CEA) T-cell bispecific (CEA CD3 TCB) antibody as a single agent and in combination with atezolizumab: Preliminary efficacy and safety in patients with metastatic colorectal cancer (mCRC)	Tabernero J, et al: J Clin Oncol 35, 2017 (suppl; abstr 3002)
	Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: Results of the phase II study CheckMate 204	Tawbi HAH, et al: J Clin Oncol 35, 2017 (suppl; abstr 9507)
	Adjuvant capecitabine for breast cancer after preoperative chemotherapy	Masuda N, et al: N Engl J Med 376:2147-2159, 2017
	Irinotecan-temozolomide with temsirolimus or dinutuximab in children with refractory or relapsed neuroblastoma (COG ANBL1221): An open-label, randomized, phase 2 trial	Mody R, et al: Lancet Oncol 18:946-57, 2017
	Hormonal maintenance therapy for women with low-grade serous cancer of the ovary or peritoneum	Gershenson DM, et al: J Clin Oncol 35:1103-1111, 2017
	A phase I study of convection enhanced delivery (CED) of 124I-8H9 radio-labeled monoclonal antibody in children with diffuse intrinsic pontine glioma (DIPG)	Souweidane MM, et al: J Clin Oncol 35, 2017 (suppl; abstr 2010)
	Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation	Stone RM, et al: N Engl J Med 377:454-464, 2017
	Phase III randomized trial of chemotherapy with or without bevacizumab (B) in patients (pts) with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN): Survival analysis of E1305, an ECOG-ACRIN Cancer Research Group trial	Argiris A, et al: J Clin Oncol 35, 2017 (suppl; abstr 6000)
	Efficacy of dabrafenib (D) and trametinib (T) in patients (pts) with *BRAF* V600E–mutated anaplastic thyroid cancer (ATC)	Subbiah V, et al: J Clin Oncol 35, 2017 (suppl; abstr 6023)
	MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR^+/$HER2^-$ advanced breast cancer who had progressed while receiving endocrine therapy	Sledge GW, et al: J Clin Oncol 35:2875-2884, 2017
Patient care	The impact of exercise on cancer mortality, recurrence, and treatment-related adverse effects	Cormie P, et al: Epidemiol Rev 39:71-92, 2017
	Traveling to a high-volume center is associated with improved survival for patients with esophageal cancer	Speicher PJ, et al: Ann Surg 265.4:743, 2017
	Temporal trends in treatment and subsequent neoplasm risk among 5-year survivors of childhood cancer, 1970-2015	Turcotte LM, et al: JAMA 317:814-824, 2017
	Measuring financial toxicity as a clinically relevant patient-reported outcome: The validation of the Comprehensive Score for financial Toxicity (COST)	De Souza JA, et al: Cancer 123:476-484, 2017
	Long-term results of a phase II randomized controlled trial (RCT) of a psychological intervention (Conquer Fear) to reduce clinical levels of fear of cancer recurrence in breast, colorectal, and melanoma cancer survivors	Beit JM, et al: J Clin Oncol 35, 2017 (suppl; abstr LBA10000)
Tumor biology	Novel molecular subgroups for clinical classification and outcome prediction in childhood medulloblastoma: A cohort study	Schwalbe EC, et al: Lancet Oncol 18:958-971, 2017
	DNA methylation heterogeneity defines a disease spectrum in Ewing sarcoma	Sheffield NC, et al: Nat Med 23:386-395, 2017

Abbreviations: ACRIN, American College of Radiology Imaging Network; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

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Use of non-ionizing electromagnetic fields for the treatment of cancer

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1. ABSTRACT

Cancer treatment and treatment options are quite limited in circumstances such as when the tumor is inoperable, in brain cancers when the drugs cannot penetrate the blood-brain-barrier, or when there is no tumor-specific target for generation of effective therapeutic antibodies. Despite the fact that electromagnetic fields (EMF) in medicine have been used for therapeutic or diagnostic purposes, the use of non-ionizing EMF for cancer treatment is a new emerging concept. Here we summarize the history of EMF from the 1890's to the novel and new innovative methods that target and treat cancer by non-ionizing radiation.

2. INTRODUCTION

In this review, we summarize current technologies that utilize non-ionizing RF EMF for cancer therapy and the existing research that may potentially elucidate the mechanisms underlying their anti-cancer effects. These include tissue heating/ablation, altered mitotic spindle formation and channel specific calcium signaling. We also discuss the development of these technologies and field of research by reviewing the history of Radiofrequency Electromagnetic Fields.

3. HISTORY OF RADIOFREQUENCY ELECTROMAGNETIC FIELDS (RF EMF)

The notion that electromagnetic radiation (see Figure 1 for EMF spectrum) could have a biological impact by releasing heat in tissues emerged in the 1890's as electricity began to be produced in a controlled form. Arsène d'Arsonval was one of the first to identify increases in temperature and metabolism of the microbial cell in contact with electricity, and then, with Albert Charrin, he reported the attenuation of diphtheria and pyocyanic toxins by radiation at a frequency of 2 x 10^3 cycles per second (200 kHz) without a significant increase in temperature (1-3). In 1924, it was shown that when tumorous plants were subjected to ultra-short wavelengths, tumors would initially grow rapidly but then completely and selectively necrose (4). Some years later, it was reported that malignant tumors in mice could be destroyed by currents of very high frequency (VHF) (5). These reports also opened a large debate over thermal, which predominate, and non-thermal effects on living tissue (6-8). This scientific research was primarily conducted in a medical environment, which was interested in therapeutic applications.

At about the same time the invention of the split-anode magnetron (1920 General Electric research laboratories, New York; Albert W. Hull) and mainly the klystron (1938 Stanford University; Varian brothers, W.W. Hausen and D.L. Webster), which generated higher frequencies and power outputs, led to the development of new microwave energy generators and expanded their potential uses (9, 10). While this was of interest to physicians at the Mayo Clinic in 1937, the power was far too low for therapeutic use. Over time the power levels began to increase and in 1938, the magnetron could produce 100 watts of power, then in 1939 it was found that the klystron could produce several hundred watts of power. As power began to reach a level high enough for therapeutic use, the magnetron and klystron became "mysteriously" unavailable (11). It was not until much later that it was discovered that the development of the magnetron and klystron were only designated for military application during World War II, in particular for radar, which did not seem harmful to personnel (12). Specifically, the development of a multicavity, air-cooled magnetron (1940 University of Birmingham, England; John Randall and Harry Boot) had been very important in perfecting radar (13). The same year, this multi-cavity magnetron was brought to the United States, after which the development of tubes that could produce a power output as high as one million watts was generated (14). The microwaves these new tubes could create had optical properties that could be reflected, refracted and diffracted. The cavity magnetron became largely used in radar technology by the Allies; the klystron being preferred by the Germans. The impact of war on research was without a doubt important.

In 1946 a microwave generator (cavity magnetron) became available to the Mayo Clinic for renewed studies on living animals (11). Much more careful investigation needed to be conducted with microwave energy to understand its way of functioning and its possible safe place in medical therapy (16). During the 1950's a considerable push was under way to examine the biological effects of microwave radiation and possible harmful effects to the human body because "they have important uses in defense projects, industrial developments, and basic physical research" (17). A 1957 report described the death of a man standing in the direct beam of a radar transmitter. It was reported that the man experienced a sensation of heat, which quickly became intolerable in less than a minute. Within 30 minutes he developed acute abdominal pain and vomiting, which prompted surgical opening of the abdomen and draining of approximately 500 cc of serosanguinous fluid with the excision of the appendix that appeared gangrenous. The post-operative course was at first good but abdominal distention recurred and inflammation of the intestines with evisceration of the wound led the patient to his death ten days after the incident (18). It reinforced considerable interest and research in the biological aspects of exposure to radio frequency electromagnetic field (RF EMF) (19). U.S. government officials and business companies, such as Chief of R&D of Ordnance Missile Laboratory, Sylvania Electric Company and Bell telephone labs, began to issue statements related to the untoward effects of high powered radar for which safety limits should be determined (1, 19). In March 1959, experiments to determine the effects of close-range exposure of the brain of a monkey to high intensity radio waves were conducted by the National Institutes of Health and reported before the House of Representatives Appropriations subcommittee. In examining the brains of ten monkeys, which died during the experiments, no pathological cause of death could be found. In a separate set of 10 monkeys whose exposure was cut short of death, the monkeys had convulsions resembling Parkinson's disease in humans (20). Another main aspect of research was to find out non-thermal non-ionizing biological effect of living tissue (21).

In 1968, James R. Hamer, reported that in 29 human subjects exposed to sinusoidal electric fields at field magnitudes of four volts per meter in the frequency range of 2-12 Hertz, reaction time performance was found to be approximately 1.6 milliseconds faster during "field on" compared to "field off" conditions. The experiments revealed that the effects were frequency sensitive and not merely due to the presence of the field (22). This work was a prime example showing that exposure to a low level, low frequency electric field could impact a biological system in a non-thermal, non-ionizing manner.

In 1969, Gavalas, Walter, Hamer and Adey reported that exposure to low-level, low frequency sinusoidal electric fields had an effect on the behavior and pattern of electrical activity (EEG) of monkey brains. Behaviorally, monkeys displayed a shorter inter response (time between signal and response behavior, i.e. push a lever in front of each subject) when exposed to 7 cycles per second but not to 10 cycles per second electric fields. EEG results showed an increase in percent power at the frequency of the fields for the hippocampus but less consistently in the amygdala and center median (the brain structures used for recording EEG and measuring percent power). Percent power is calculated by averaging spectral intensity and coherences for each brain structure. The "Coherence," parameter is calculated by analyzing the coherence between the imposed field and the activity in each structure, as well as between the brain structures themselves. The "Spectral intensity," is a specialized statistical test for the effect of the imposed field on recorded activity. The increased percent power, in some brain structures, was observed during two

different conditions, one being 7 cycles per second and the other being 10 cycles per second, a previously reported frequency exposure used by Hamer and identified to have an effect on human reaction time (23).

In 1973 Bawin, Gavalas-Medici and Adey studied the effects of exposures to low intensity, very high frequency (VHF-147 MHz) electromagnetic fields, amplitude-modulated at biologically relevant frequencies (1-25 Hz) on cats with chronically implanted electrodes. To minimize interference with VHF fields due to behavioral responses and/or gross body movements, cats underwent pattern conditioning of specific brain locations. This was accomplished by directly conditioning specific patterns in specific brain locations which would then allow consideration of the overt behavior as a correlate of the conditioned response (24). The authors found that low level VHF, amplitude-modulated at specific frequencies, produced marked effects on conditioned specific brain rhythms (enhanced regularity of patterns, sharpening of the spectral peaks around the central frequency of the response, extremely prolonged resistance to extinction). This work brought attention to the realm of non-thermal biological response to EMF by showing changes in brain wave patterns. Up until this time, much of the work had been accomplished by Russian and Eastern European investigators, although Gavalas et al., 1970, may have been first to report changes in brain electrical activity (23, 24). Building on their previous work, in 1975, Bawin et al. identified enhanced calcium efflux from chick brain tissue in a test tube following exposure to amplitude-modulated (AM) radio frequency (RF) waves. This effect appeared to occur without involvement of heating and appeared to be mediated by release of calcium. Specifically, the radiofrequency-dependent calcium efflux from chick brains was only reported when a carrier wave (147 MHZ) was sinusoidally amplitude-modulated (see Figure 2 for example of amplitude modulation) at specific frequencies of 6, 9, 11, 16, and 20 Hz. No altered efflux compared to control was found without modulation nor at 0.5., 3, 25 or 35 Hz modulations (25). Another, more limited report by the Bawin group show that 450 MHz EMF, amplitude modulated at 16 Hz, enhanced calcium release in a narrow window of intensities (26). Additionally, when chick brains were co-treated with cyanide (a compound which prevents electron transport in the cytochrome, shutting down metabolism) calcium efflux still occurred, which indicates that amplitude modulation-dependent calcium efflux does not depend on metabolic processes. These findings provided the experimental basis that suggested a molecular mechanism explaining Bawin et al.'s (1973) work on the inhibition and excitation of the cerebral cortex of cats, as well as the work of Hamer, Gavalas, and Subbota (22,25,27, 28).

On the heels of Bawin's work, the focus began to turn to the molecular mechanism behind EMF exposure effects on biological systems and the understanding that EMF demodulation could explain such a mechanism.

In 1980 Blackman et al. independently reproduced the work of Bawin et al. by showing that calcium efflux from chick brains occur in a windowed, sinusoidally amplitude-modulated, frequency-specific fashion (32). Moreover, Blackman built on the research performed by Bawin et al. and showed that calcium efflux depends on specific amplitude-modulations independently of the carrier wave (50 MHz). Importantly, Blackman et al. validated specific "modulation frequency windows" at which calcium efflux occurred. They also demonstrated that such effects only occurred within certain levels of power exposure and were amplitude-modulation dependent; an effect first identified by Bawin et al (1975) (25,33, 34).

In 1984 Dutta et al. published work focusing on calcium ions and their relationship to microwave radiation (915 MHz) with or without sinusoidal, amplitude-modulation (80%) at 16 Hz at various specific absorption rates (SAR). They found that in human neuroblastoma cells (IMR-32) calcium efflux occurred in a power and amplitude-modulation frequency-specific fashion. Specifically, a significant efflux of calcium ions was found to occur at two SAR values 0.05 and 1 mW/g of an amplitude-modulated (16Hz AM) microwave (915 MHz-carrier wave) compared to unexposed samples further validating the work of Bawin, Adey, Blackman, and Joines (35). An additional validation of this phenomenon was provided in 1990 by Schwartz who reported enhanced calcium ion release from isolated, beating frog hearts only when they were exposed to 240 MHz EMF, sinusoidally amplitude modulated at 16 Hz, but not when exposed at 0.5 Hz nor when the EMF was unmodulated (36).

The research and development of EMF in biological systems has now spanned over 100 years, from d'Arsonval to World War II to calcium efflux, and now we are beginning to see the rise of therapeutic non-thermal, non-ionizing EMF exposure. In this review we highlight some of the most innovative and promising therapeutic research currently being performed in the field of cancer.

4. MINIMALLY-INVASIVE RF EMF FOR THERAPEUTIC USE IN CANCER

4.1. Nano-Radio-Frequency Ablation (NaRFA)

Non-ionizing radio frequency (RF) radiation is a common thermal therapy approach used in clinical oncology (37).In particular, radiofrequency ablation's (RFA) approach of hyperthermia (temperatures above 47 ^{o}C) will expose target tissue to high temperatures to destroy the tissue directly or render cancer cells more susceptible to other treatment modalities (thermal sensitization; 41- 45 ^{o}C) (37) (Table 1). While this technique does show success, RFA is a localized and invasive method that requires a needle to penetrate directly into the tumor. Even though this technique is very effective and widely used, specifically for the treatment of hepatic (primary or metastatic), kidney, liver and a number of other neoplasms, this indication is limited by tumor size and tumor location (38, 39). Close proximity of the tumor to the biliary tree or blood vessels is considered a contraindication to its use. Moreover, targeting a localized tissue and selecting an appropriate or efficient method of heat delivery remains an issue. Multiple sources of energy

for heat delivery include microwaves, radiofrequency, laser and ultrasound (37). Here we briefly summarize a few novel uses of radio frequency exposure as a method of localized RFA using nano-particles.

Nano-Radio-Frequency Ablation (NaRFA) is an experimental method of non-invasive RFA with the potential to improve the efficacy of thermal damage to tumors while minimizing damage to normal healthy tissues. In order to accomplish this, tumors are loaded with nanoparticles that enhance the conversion of external energy source (RF) into heat, creating an inside-out hyperthermia. This is possible because RF fields are able to penetrate deep into the body without the need for an invasive procedure (37). One such example of NaRFA is carbon based nanomaterials. Single-walled carbon nanotubes (SWNTs) can be modified to increase efficacy by improving specificity through surface engineering of SWNTs to have ligands, which can target receptors specific to cancer cells (40, 41).In a study performed by Gannon et al. RF exposure of SWNT caused cytotoxicity of cancer cells in vitro and in vivo while being well tolerated by rabbits bearing tumors. A second example can be found in Carbon coated metallic nanoparticles (C-Co-NPs). C-Co-NPs are 7-nm cubic crystalline graphitic carbon decorated ferromagnetic cobalt nanoparticles (40).These nanoparticles have been shown to effectively enter HeLa cells and when exposed to RF pulses of 350 kHz the nanoparticles generate localized heat, a process that is dependent on RF power and nanoparticle concentration. The treated HeLa cells showed DNA fragmentation, nucleus rupturing and membrane disintegration (40).An additional example is found in the work of Tamarov et al. and their use of crystalline silicon (Si) based nanomaterials. An aqueous suspension of Si nanoparticles is able to generate temperatures above 45-50 ^{o}C when exposed to 27 MHz RF EMF (41).Moreover, Si nanoparticles are biocompatible and biodegradable in biological tissues, decaying into orthosilicic acid, $Si(OH)_4$, which will be voided through the urinary tract. In vivo work displayed inhibition of tumor growth and led to a decrease in tumor volume (42).

4.1.1. Mechanism of Action for Nano-Radio-Frequency Ablation (NaRFA)

Heat generation in nanoparticles when exposed to low RF fields remains a contentious subject (37, 43).The dominant mechanism behind RF heating is joule heating (heat released due to resistivity of nanoparticle; Power (P) is dissipated in the form of heat, and given I is electric current and R is resistance, $P = I^2R$). No optimal RF conditions for effective heating have been reported and power has been reported to range from 40-800 W (37, 40, 44).A number of other factors such as electrical conductivity, size, shape, and concentration of the nanoparticles contribute to heating effects as well (37).While systems such as NaRFA appear to be promising it should be noted that there is a need for more in vivo, clinical data as well as technological refinement to reduce unwanted tissue damage and increased specificity of the nanomaterial to the target (37, 40).Moreover, there are currently at least two other separate RF technologies in existence that have no need for nanoparticles and have shown beneficial activity in cancer patients.

4.2. TheraBionic^{TM}: Tumor-Specific AM RF EMF

During the 1990's Pasche et al. demonstrated that intrabuccal administration of low and safe levels of 27.12 MHz RF EMF, amplitude-modulated at 42.7 Hz, has a sleep-inducing effect in healthy patients but does not improve sleep in patients with a diagnosis of insomnia (45, 46).However, when patients with a diagnosis of insomnia were treated with the same carrier signal amplitude-modulated at four different frequencies (2.7 Hz, 21.9 Hz, 42.7 Hz and 48.9 Hz; i.e. insomnia-specific modulation) they experienced shorter sleep latency, longer total sleep time, increased sleep efficiency, and increased numbers of sleep cycles compared to controls (47, 48).In early 2000, Pasche and Barbault hypothesized that tumor-specific modulation frequencies could be used to treat cancer. In 2009, Barbault et al. published the results of their investigations to determine if tumors may be sensitive to specific RF EMF modulated at specific frequencies. Using devices emitting a carrier frequency of either 433 MHz or 27 MHz the authors exposed 163 patients, who had a diagnosis of cancer, to RF EMF amplitude-modulated in the range of 0.1Hz to 114 kHz and the results of the study were remarkable (49). The authors reported that patients with cancer, but not healthy patients, had changes in skin electrical resistance, pulse amplitude and blood pressure (biofeedback responses) when exposed to a subset of very discrete modulation frequencies. Interestingly, patients with the same tumor type were found to exhibit biofeedback responses when exposed to the same discrete modulation frequencies creating a frequency set specific to tumor type. Moreover, the majority of frequencies found for any given tumor type were specific to that tumor type only and only 4 frequencies (1873.5 Hz, 2221.3 Hz, 6350.3 Hz and 10456.4 Hz) were found to overlap in multiple tumor types specifically, breast cancer, hepatocellular carcinoma, prostate cancer and pancreatic cancer (49).Post frequency identification, the authors then proposed to determine if treatment with the recently discovered tumor-specific frequency sets to corresponding cancer patients would have a therapeutic effect and hence the authors offered compassionate treatment to patients with limited therapeutic options. Again, the results were remarkable, of sixteen patients evaluable for response, one patient with hormone-refractory breast cancer metastatic to the adrenal gland and bones had a complete response lasting 11 months. One patient with hormone-refractory breast cancer metastatic to liver and bones had a partial response lasting 13.5 months, Four patients had stable disease lasting more than: 7 years (thyroid cancer metastatic to the lung), 5.1 months (non-small cell lung cancer), 4.1 months (pancreatic cancer metastatic to liver) and 4.0 months (leiomyosarcoma metastatic to liver) (15, 49).These results indicate that treatment not only has an impact on the primary tumor but can also treat metastatic tumors implying that this treatment is systemic.

Building upon their findings from 2009, Costa et al. conducted a single-group; single-center, open-label, phase I/II study in patients with advanced hepatocellular carcinoma (HCC). In this study, more than 75% of patients had radiological evidence of disease progression and half of the patients had poor liver function with limited treatment options at the time of treatment initiation. All patients were exposed to electromagnetic fields amplitude modulated at

HCC-specific frequencies. A total of 41 patients with advanced HCC and Child Pugh A or B disease were accrued and self-administered treatment three times daily for 60 minute (180 min) until disease progression or death and imaging studies were obtained every eight weeks. The results supported the initial experience with the same device: four patients had objective tumor response. One patient with prior progressive disease experienced durable near complete response lasting more than 5 years, and fourteen patients had stable disease for more than 6 months. The median progression-free survival (PFS) was 4.4 months (95% CI: 2.1-5.3) and median overall survival (OS) was 6.7 months (95% CI: 3.0-10.2). Subset analysis of the patients with similar diagnostic criteria as those applied in phase III studies such as the SHARP and Asia-Pacific sorafenib studies (Llovet et al., 2008;Cheng et al., 2009), i.e. biopsy-proven disease and assessment of disease with CT, shows an objective response rate (RR) by RECIST of 18.2.% (2/11), and median PFS and OS of 4.9 months (95% CI .6 to 10.8 months) and 10.8 months (95% CI 2.1 to 34.0 months) (50, 51).Overall, there were six long-term survivors with an OS greater than 24 months and four long-term survivors greater than three years. Despite long-term treatment duration and poor liver function in the majority of patients, treatment was well tolerated and no NCI grade 2, 3, or 4 toxicities were reported (31).

To further evaluate the results found by the work of Barbault et al. (2009) and Costa et al. (2011), Zimmerman et al. (2012) performed in vitro studies to begin to elucidate the mechanism of this novel therapy. Using specifically designed exposure devices to replicate the clinical exposure settings, Zimmerman et al. investigated whether the proliferation of HCC (HepG2 and Huh-7), breast cancer (MCF-7) and corresponding non-malignant THLE-2 (represent normal liver cells), MCF-10A (represent normal breast cells) cell lines would be affected by the tumor-specific modulation RF EMF that were found in the clinical setting. Using tumor-specific RF EMF vs control exposure, comprised of randomly chosen modulation frequencies within the same range as cancer-specific frequencies, authors found that tumor-specific frequencies were able to inhibit the proliferation of cancer cells when used in a corresponding fashion i.e. HCC-cell lines exposed to HCC-specific frequencies. Yet, when HCC-specific frequencies were used on breast cancer cells, or vice versa, no proliferative inhibition was noted. Furthermore, HCC-specific and breast cancer-specific frequencies did not inhibit the proliferation of THLE-2 or MCF-10A cells, respectively. These findings led to the conclusion that exposure to tumor-specific RF EMF not only had an inhibitory effect on the proliferation of cells but that it did so in a cancer-specific fashion, apparently not affecting normal healthy cells (15, 52).The authors also discovered that mitotic spindle formation was greatly disrupted in HCC-specific treated HepG2 cell and genes relating to migration (PLP2) and invasion (XCL2) were found to be significantly downregulated as shown via RNA-seq and confirmed by qPCR (52).The exact mechanism of action of this new therapeutic approach is unknown.

4.3. Novocure™

NovoTTF-100A (brand name Optune®) is a device that delivers low-magnitude (1-3 V/cm), intermediate frequency (100-300 kHz) tumor treating electric fields (TTFields) by transducer arrays that are applied directly to the scalp (53-55).The Novo TTF-100A system slows tumor growth and inhibits mitosis. More specifically, TTFields have been shown to disrupt glioblastoma cells during mitosis, resulting in apoptosis, aneuploidy, asymmetric chromosome segregation, and defects in centrioles and mitotic spindles. Additionally, TTFields causes cytoplasmic stress which targets tumor cells for immunological destruction and clearance TTFields have been demonstrated to inhibit proliferation in multiple cancer cell lines, e.g., human melanoma, lung, prostate, pancreas, breast and glioma after 24 hours of continuous exposure while not having any impact on normal non-dividing cells (53, 54).In addition, mice bearing tumors (mouse melanoma and rat glioma) also showed growth inhibition and a decrease in angiogenesis after less than one week of treatment.

Optune® is approved by the U.S. FDA for use as a treatment for adult patients with histologically-confirmed glioblastoma (55).The activity of TTFields is intensity and frequency specific and is inversely proportional to tumor cell size. Hence, the NovoTTF device can be optimized for multiple tumor types such as pancreas adenocarcinoma, ovarian cancer and non-small cell lung cancer (54).Of importance, the device and treatment is considered to be safe as normally dividing cells would require a different frequency set to have mitotic interference making the TTFields specific to dividing cancer cells (54).Due to the effects of the TTFields being directional (TTF fields function best when applied in the direction of the separation axis of the dividing cell) two sequential field directions are applied to patients by wearing two pairs of transducer arrays that generate fields that switch direction by 90°.Lastly, TTFields do not attenuate over distance(s) used in treatment and are minimally impacted by biological tissues. This gives TTFields the capability to cover large body regions that may be commonly affected by metastases deep within organs, so long as the leads are placed over the metastatic area. The clinical recommended treatment time is a minimum of 18 hours continuous treatment per day (54).

In 2014, the Data Safety Monitoring Board recommended that the Phase III clinical trial of this device in patients with newly diagnosed glioblastoma be stopped after it was reported that during the interim analysis of 315 patients who received standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy resulted in significant improvements in progression-free survival (PFS) and overall survival (OS) (56).Specifically, median PFS in the intent–to–treat population was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group; hazard ratio (HR) 0.62; (98.7% CI, 0.43-0.89); P = 0.001). The median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFields plus temozolomide group (n=196) and 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group (n=84); HR 0.64 (99.4% CI, 0.42-0.98); P=0.004) (56).

4.3. 1. Novocure™ TTF (Tumor treating fields) Mechanism

The use of intermediate-frequency electric fields (kHz-MHz range) alternate too fast to cause nerve-muscle stimulation and involve a minimal amount of heating; until the mid-2000's fields in this range were generally accepted as having no biological effect (54, 57).The mechanism of action involves destabilization of spindle microtubules, consequently leading to mitotic catastrophe. It is unknown whether this effect occurs by direct interference of the addition of tubulin subunits to microtubules or by destruction of existing microtubules structures (57).Hence, cells entering mitosis are those most likely to respond to treatment and would exclusively impact dividing cells (54, 57).Additionally, after spindle disruption by TTFields, and the prolonged mitotic arrest that may occur, subsequent cell death is more likely the outcome than mitotic arrest and yet it is still not understood what initially triggers the caspase dependent apoptosis. Data generated by Giladi et al. suggests that the accumulation of significant aneuploidy, in tandem with mitotic arrest, contributes to the compromised viability of cancer cells (57).

5. NOVOCURE™ AND THERABIONIC™: TWO NOVEL MODALITIES FOR CANCER TREATMENT

The mechanism(s) of action for RF EMF on biological systems beyond heating have not been fully established. Hence, we discuss published research that will have important biological relevance to the likely mechanistic difference that may underlie two distinct therapeutic options offered by Novocure's TTF-100A (Optune®) and the Therabionic™ device.

5.1. Relevant Literature for Novocure/Optune®

Novocure™'s Optune® identified the improper formation of microtubules as key to the inhibitory action on GBM. In literature relevant to the intracellular mechanics of centrioles the presence of electromagnetic forces is evident (58).Microtubules are hollow cylinders composed of 13 longitudinal filaments. The filaments are strings of alpha/beta tubulin dimers connected end to end with the alpha/beta tubulin dimers having positive and negative charges at their ends. During filament movement, by means of their vibration, oscillation of these charged dimers produces an electromagnetic field (58).Evidence of cellular electromagnetic field activity occurs during mitosis when centriole pairs are separated to diametrically opposite sides of the nucleus and extend out microtubules toward each other to begin the separation the cell in two (58).This electromagnetically active area certainly appears to continue to be a prime target for Novocure™'s treatment and future research.

5.2. Relevant Literature for Therabionic™

The work described in the 2009 Barbault et al. paper reports that discovery of frequencies, used in the treatment of cancer, was based on the measurement of variations in skin electrical resistance, pulse amplitude and blood pressure (49).Calcium (Ca^{2+}), Ca^{2+} signaling and Ca^{2+} channels are an important feature of blood pressure regulation and cardiovascular health. Here we highlight the work performed by Buckner et al. that potentially sheds light on the work related to calcium ion channels (59, 60).The studies performed by Buckner et al. show that exposure to a specially designed, weak (2-10 μTesla), frequency-modulated, patterned EMF signal called the Thomas-EMF signal, can inhibit the growth of malignant cells by promoting Ca^{2+} uptake through T-type voltage-gated calcium channels (VGCC) (61).This effect does not appear to be mediated by L-type voltage-gated calcium channels (61).The Thomas-EMF pattern is a digital file composed of 849 points programmed to deliver each point for 3 milliseconds. Exposure to the Thomas-EMF pattern at various time intervals has been previously associated with an analgesic response, an outcome whose mechanism was suspected to be due to or include metal binding ions (Ca^{2+} and K^+) (62).Additionally, the Thomas-EMF pattern was designed to affect membrane activity associated with epileptic seizures, a disease state known to be related to alterations in various types of ion channels (Ca^{2+}, K^+, Na^+, GABA) (61-63).Buckner et al. exposed cultured cells of mouse and human origin (B16-BL6, MDA-MB-231, MCF-7, HSG, HBL-100, HEK293 and HeLa) or mice (bearing tumors from hind flank injected B16-BL6 cells) to Thomas-EMF signal (2-10 microT). Proliferative inhibition was found to occur in malignant cells only, e.g., MDA-MB-231, MCF-7 and HeLa cells and in mice bearing tumors whereas non-malignant cells, e.g., HBL-100, HEK293 and HSG cells were unaffected. In attempting to understand the mechanism for proliferative inhibition Buckner et al. reported that in malignant cells an increase in Ca^{2+} influx occurred, specifically through the T-type VGCC while in non-malignant cells no increase in Ca^{2+} influx was found. Moreover, blocking Ca^{2+} influx with T-type VGCC blockers appeared to block the ability of Thomas-EMF signal to inhibit cell proliferation. Additionally, malignant cells, exposed to Thomas-EMF signal, also showed a slowed entry into the S-phase of the cell cycle as noted by temporal changes in cyclin expression but, did not show cell death or DNA fragmentation (61).Hence, Buckner et al. concluded that specific EMF patterns can affect biological systems by allowing for increased cytoplasmic Ca^{2+} which then impacts the cell cycle by changes in cyclin expression (61, 64, 65).This provides a potential anti-cancer therapy that acts through the T-type VGCC to allow inappropriate influx of Ca^{2+} resulting in proliferative inhibition (61).

The research reports published by Buckner et al. appear to have relevance to Therabionic's cancer treatment, particularly given the fact that their initial focus of work was on the treatment of insomnia, a disease state that can be mediated by Ca^{2+} and T-type VGCC dysregulation (48, 66, 67).Moreover, enhanced Ca^{2+} flux has been shown to be affected by RF exposure in research that dates as far back as the 1970s and in a modulation specific fashion (68-72).Hence, hypothetically, amplitude-modulated RF exposure eliciting a calcium dependent anti-cancer specific response could represent a promising, if not paradigm changing, direction in the treatment of cancer (30).

6. CONCLUSION

In closing, with the number of tumor types currently under investigation with the Novocure^{TM} technology combined with the tumor types in which Therabionic^{TM} has already shown some efficacy, treatment, either local or systemic, of tumors with electromagnetic fields should still be considered in its infancy. Moreover, as a field of research, we expect that these technologies will quickly expand over the next ten years to become possibly as common place as chemotherapy with the hope that at the very worst it will allow cancer to become a chronic condition instead of a life-ending disease.

7. ACKNOWLEDGEMENT

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Functional Biological Activity of Sorafenib as a Tumor-Treating Field Sensitizer for Glioblastoma Therapy

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Abstract: Glioblastoma, the most common primary brain tumor in adults, is an incurable malignancy with poor short-term survival and is typically treated with radiotherapy along with temozolomide. While the development of tumor-treating fields (TTFields), electric fields with alternating low and intermediate intensity has facilitated glioblastoma treatment, clinical outcomes of TTFields are reportedly inconsistent. However, combinatorial administration of chemotherapy with TTFields has proven effective for glioblastoma patients. Sorafenib, an anti-proliferative and apoptogenic agent, is used as first-line treatment for glioblastoma. This study aimed to investigate the effect of sorafenib on TTFields-induced anti-tumor and anti-angiogenesis responses in glioblastoma cells in vitro and in vivo. Sorafenib sensitized glioblastoma cells to TTFields, as evident from significantly decreased post-TTFields cell viability ($p < 0.05$), and combinatorial treatment with sorafenib and TTFields accelerated apoptosis via reactive oxygen species (ROS) generation, as evident from Poly (ADP-ribose) polymerase (PARP) cleavage. Furthermore, use of sorafenib plus TTFields increased autophagy, as evident from LC3 upregulation and autophagic vacuole formation. Cell cycle markers accumulated, and cells underwent a G2/M arrest, with an increased G0/G1 cell ratio. In addition, the combinatorial treatment significantly inhibited tumor cell motility and invasiveness, and angiogenesis. Our results suggest that combination therapy with sorafenib and TTFields is slightly better than each individual therapy and could potentially be used to treat glioblastoma in clinic, which requires further studies.

Keywords: tumor-treating fields; glioblastoma; sorafenib

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1. Introduction

Glioblastoma, the most common primary brain tumor in adults, remains an incurable malignancy with a short expected survival [1]. For a long time, glioblastoma treatment included surgical cytoreduction followed by radiotherapy [2]. With this approach, the median survival was approximately 10 to 12 months [3,4]. In a recent study, co-administration of temozolomide (TMZ) with radiotherapy yielded better outcomes than radiotherapy alone [1]. With this new treatment standard,

the expected median survival is 14.6 months, with a 2-year survival rate of 26.5% [5]. Tumor-treating fields (TTFields), alternating electric fields with a very low intensity (<2 V/cm) and an intermediate frequency (100–300 kHz), disrupt mitotic spindle formation during metaphase and effectively inhibit the growth of various human tumor cell lines, and have therefore been proposed to be useful in cancer treatment [6]. Accurate alignment of tubulin and septin is required for the initiation of cell division; this may be disrupted by TTFields [7]. Consequently, cancer cells in a G2/M arrest can be eliminated. Thus, TTFields have more pronounced effects on rapidly dividing cancer cells than on normal cells, implying that cancer cells can be selectively damaged. Another hypothesis regarding the mechanism underlying TTFields is the occurrence of chromosomal anomalies due to the inhibition of spindle formation by TTFields [8]. Chromosomal aberrations such as missegregation resulting from cell division can lead to apoptosis [9]. Furthermore, TTFields reportedly inhibit the localization of the septin complex, thereby disrupting cell division [7,10]. Recent clinical studies have reported that treatment of recurrent glioblastoma patients with TTFields may lead to longer overall survival than that observed with standard treatment, with no unexpected side effects [11]. In contrast, a randomized clinical trial reported that the outcomes for recurrent glioblastoma patients administered TTFields were not significantly better than those for patients administered conventional therapy [12]. The use of TTFields in combination with chemotherapeutic drugs increased the survival rate, without an increase in toxicity, compared with chemotherapy lone in a recent randomized clinical trial in newly diagnosed glioblastoma patients [13]. Previous studies have suggested that, although the clinical effectiveness of TTFields alone remains controversial, combinatorial therapy with TTFields and chemotherapy or radiotherapy are more efficient than monotherapy for newly diagnosed glioblastoma patients [14].

One potential chemotherapeutic agent for glioblastoma, sorafenib, is an oral multikinase inhibitor that blocks tumor cell proliferation and angiogenesis and induces tumor cell apoptosis by inhibiting serine/threonine kinases (c-RAF, and mutant and wild-type BRAF) and receptor tyrosine kinases, such as vascular endothelial growth factor receptors 2 and 3 (VEGFR2 and VEGFR3), platelet-derived growth factor receptor β (PDGFRβ), FLT3, and c-KIT [15]. In addition, sorafenib inhibits the mitogen activated protein kinase (MAPK)/extracellular-signal-regulated kinase (ERK) pathway, which plays an important role in cancer cell development [16,17], and inhibits eIF4E phosphorylation and downregulates Mcl-1 [17]. Sorafenib reportedly induces autophagy via LC3 upregulation, which occurs during autophagy and autophagy-related processes, including autophagic cell death [18–20]. Evaluation of sorafenib in phase I and II clinical trials on several forms of advanced solid tumors revealed favorable tolerability and promising clinical antitumor activity in advanced renal cell carcinoma, hepatocellular carcinoma, thyroid cancer, and osteosarcoma [21–26]. Moreover, clinical studies have used sorafenib in combination with various anticancer agents to treat several solid tumors [22]. The treatment efficacy of sorafenib with radiotherapy and temozolomide in glioblastoma patients has been investigated [27]. A desirable activity profile, preclinical evidence of antitumor activity in human malignant glioma models, and a promising safety profile have paved the way for recent phase I/II clinical trials in patients with malignant gliomas. Although phase I/II clinical trials have been conducted with sorafenib in combination with drugs such as temozolomide, bevacizumab, and temsirolimus, the therapeutic efficacy has not improved significantly [2,28,29]. Thus, sorafenib, a molecular targeting agent, and TTFields, a novel treatment modality, can be promising therapeutics that disrupt molecular defects in signaling pathways and may provide clinical benefits in treating glioblastomas.

This study aimed to investigate the mechanisms underlying the enhancement of TTFields-induced antitumor and anti-angiogenesis effects of sorafenib on glioblastoma. Our study provides a scientific rationale to evaluate this combinatorial strategy in clinical trials for TTFields therapy.

2. Results

2.1. Cooperative Effect of TTFields and Sorafenib on Glioblastoma Cancer Cell Proliferation

To determine the optimal TTFields voltage, we subjected U373 and U87 cells to various voltages for 48 h (Figure 1A). The two glioblastoma cell lines exhibited a voltage-dependent reduction in cell viability (approximately 20% at 0.9 V/cm). To evaluate the effect of sorafenib on glioblastoma cells by the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) assay, U373 and U87 cells were treated with sorafenib at different concentrations (Figure 1B). After 48 h, cell growth was significantly inhibited in cells treated with ≥5 μg/mL sorafenib ($p < 0.05$). These data indicated that U373 and U87 cells display dose-dependent sensitivity to sorafenib. In addition, the combination of sorafenib and TTFields treatment had a significantly greater antitumor effect on the U373 and U87 cells than either treatment alone, as evident from Trypan Blue and MTT cell viability assays (Figure 1C,D). Additionally, the colonies formed by mono-treated 3D cultures were larger than those formed upon combinatorial treatment (Figure 1E). In a colony formation assay, the surviving fractions decreased further in cells treated with TTFields plus sorafenib than in cells administered either of these treatments (Figure 1F). These data indicated that sorafenib has a TTFields-sensitizing effect on glioblastoma cells in vitro.

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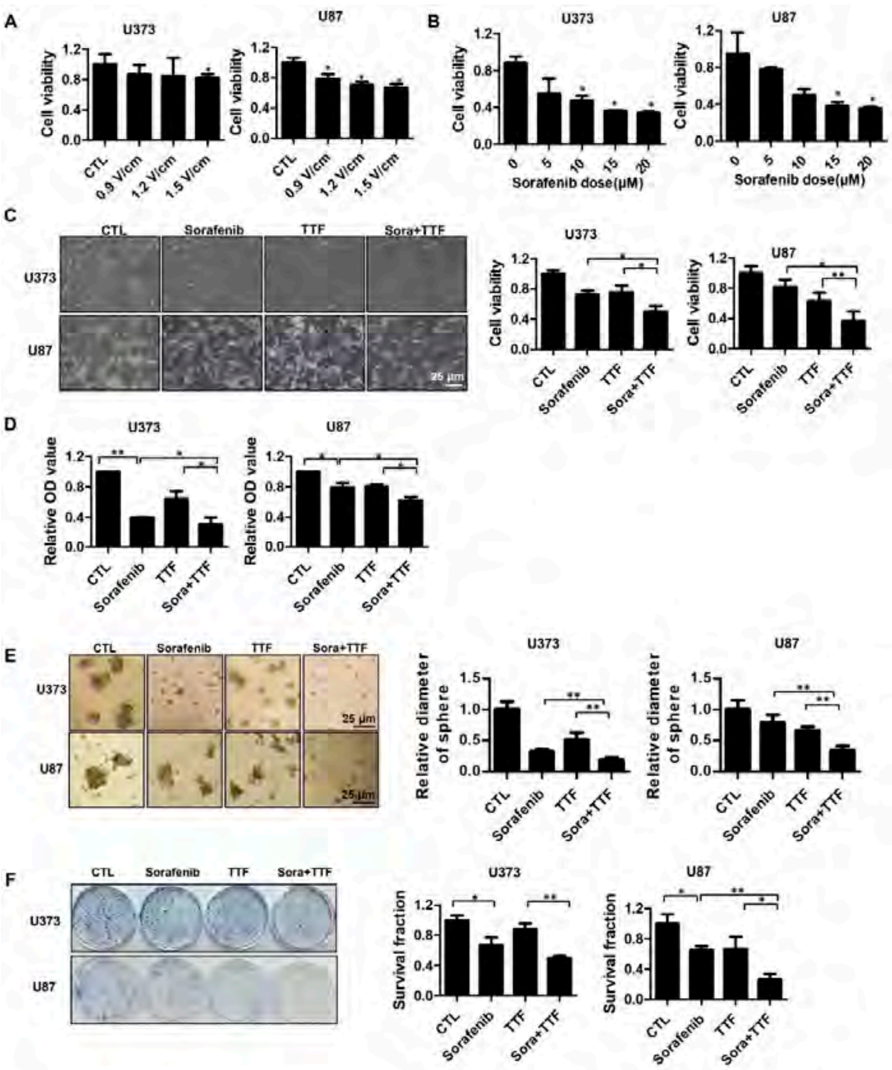

Figure 1. Tumor-treating field (TTField)-sensitizing effects of sorafenib in vitro models of glioblastoma.

glioblastoma. (**A**) TTFields inhibited glioblastoma cell viability in an intensity-dependent manner.

(**A**) TTFields inhibited glioblastoma cell viability in an intensity-dependent manner. Cell viability was evaluated by cell counting using 0.4% Trypan Blue stain for U373 and U87 cells treated with TTFields for the indicated durations; * $p < 0.05$; (**B**) sorafenib inhibited glioblastoma cell Fluorine-18viability in a dose-dependent manner. Cell viability was evaluated by cell counting using 0.4% Trypan Blue stain for U373 and U87 cells treated with the indicated doses of sorafenib; * $p < 0.05$. (**C**–**E**) the viability of cells treated with a combination of TTFields and sorafenib was significantly lower than that of cells treated with either sorafenib or TTFields. The proliferation rate was detected by counting (**C**), MTT assay (**D**), and 3D colony culture (**E**). * $p < 0.05$; ** $p < 0.01$; (**F**) the sensitivity of U373 and U87 cells treated with sorafenib and TTFields was measured via a colony formation assay. The survival fraction, which was expressed as a function of the irradiation dose, was calculated as follows: survival fraction = colonies counted/(cells seeded $\times$ plating efficiency/100). * $p < 0.05$; ** $p < 0.01$. CTL: Control group; TTF: Tumor treating fields group.

2.2. Sorafenib Promotes TTFields Sensitivity In Vivo

To assess the effect of TTFields combined with sorafenib on glioblastoma growth in vivo, we used a subcutaneous glioblastoma model generated by injecting human U373 cells into mice. As shown in Figure 2A, xenografts treated with a combination of TTFields and sorafenib displayed decelerated growth compared to the control group and the groups receiving either of the treatments. Thus, tumors in the mono-treated groups were significantly larger than those in the group receiving combinatorial treatment (Figure 2B). Concurrently, tumor weight was reduced in the mice receiving combinatorial treatment compared to that in mice receiving either of the treatments (Figure 2C). As shown in Figure 2D, low uptake of [Fluorine-18(18F)]-fluorodeoxyglucose (FDG) was observed in tumors treated with TTFields plus sorafenib as compared to tumors receiving either of the treatments. The maximum standard uptake value was 0.53 ± 0.09 in the control group, 0.39 ± 0.07 in the sorafenib-treated group, 0.38 ± 0.19 in the TTFields-treated group, and 0.28 ± 0.03 in the combination-treated group (Figure 2D). Xenografts of mice receiving either of the treatments showed more intense Ki67 staining than those of mice receiving combinatorial treatment (Figure 2E). There were no visible signs of toxicity from TTFields or sorafenib administration in the mice, as evident from the absence of differences in body weight and the weights of various organs, including the spleen, lungs, and liver (Figure 2F,G). Together, these data suggested that TTFields combined with sorafenib inhibits the growth of glioblastoma in vivo.